DOCUMENT RESUME

ED 155 297 UD 018 356

TITLE	Proceedings of the First National Sickle Cell Educational Symposium (May 1976, St. Louis, Missouri).
INSTITUTION	Public Health Service (DHEW), Arlington, Va.
REPORT NO	DHEW-NIH-78-1084
PUB DATE	78
NOTE	183p.
EDRS PRICE	MF-$0.83 HC-$10.03 Plus Postage.
DESCRIPTORS	*Blacks; *Conference Reports; Genetics; *Health Education; *Medical Case Histories; Medical Research; Medical Treatment; Social Services; *Special Health Problems
IDENTIFIERS	*Sickle Cell Anemia

ABSTRACT

This conference was organized around presentations about the cases of an adult and a pediatric sickle cell anemia patient. Following the presentations of the patients' case histories, and clinical and laboratory findings, the cases were discussed by specialists from various areas of expertise. Among the perspectives offered were those of internal medicine, hematology, ophthalmology, endocrinology, genetics, pediatrics, cardiology, nursing and social work. A series of symposia were conducted on the topics of clinical management, genetic counseling, educational techniques and current research relating to sickle cell disease. Also addressed were the need for and approach to parent education; some educational techniques; international perspectives on sickle cell disease; and the importance of education and sickle cell services as a part of comprehensive health. In addition to the full texts of the conference discussions and presentations, a list of participants is included in this report. (Author/GC)

****
* Reproductions supplied by EDRS are the best that can be made *
* from the original document. *
****

ED155297

Proceedings of the First National SICKLE CELL Educational Symposium

May, 1976
St. Louis, Missouri

U S DEPARTMENT OF HEALTH, EDUCATION & WELFARE
NATIONAL INSTITUTE OF EDUCATION

THIS DOCUMENT HAS BEEN REPRODUCED EXACTLY AS RECEIVED FROM THE PERSON OR ORGANIZATION ORIGINATING IT. POINTS OF VIEW OR OPINIONS STATED DO NOT NECESSARILY REPRESENT OFFICIAL NATIONAL INSTITUTE OF EDUCATION POSITION OR POLICY

Sponsored by
Sickle Cell Disease Branch
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
and
Office of Continuing Medical Education
Washington University School of Medicine
St. Louis, Missouri

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

DHEW Publication No. (NIH) 78-1084

UD018356

CONTENTS

Preface vii

Introduction

Clarice D. Reid, M.D. 1

Keynote Address

History of the National Sickle Cell Program
Robert I. Levy, M.D. 5

Formal Presentation

Sickle Cell Anemia: "The Great Masquerader"
Helen Ranney, M.D. 11

Grand Rounds: Pediatric Case

Presentation of the Pediatric Case
Marilyn H. Gaston, M.D. 21

The Geneticist's Perspective
Robert F. Murray, M.D. 25

The Hematologist's Perspective
Helen Ranney, M.D. 30

The Pediatrician's Perspective
Darleen Powars, M.D. 31

The Cardiologist's Perspective
William F. Friedman, M.D. 36

The Nurse's Perspective
Sylvia L. Lee, P.H.N. 38

The Social Worker's Perspective
Delores Duncan, M.S.W. 41

Discussion 43

Formal Presentation

The Need for and an Approach to Parent Education
Charles Whitten, M.D. 53

Discussion
Howard Pearson, M.D. -- moderator 61

Mini-Symposia

Clinical Management

Impairing the Switch From the Gamma Chains of Hemoglobin After the Beta Chains of A
Helen Ranney, M.D. 67

Results of a Double-Blind Clinical Trial of Oral Sodium Cyanate in Patients with Sickle Cell Anemia
Donald R. Harkness, M.D. 70

Experimental Approaches to Therapy and Sickle Cell Anemia -- Urea and Alkali
Robert S. Rhodes, M.D. 78

Theoretical Approaches to the Treatment of Sickle Cell Diseases
Donald R. Harkness, M.D. 80

Discussion 87

Genetic Counseling

Counseling Format and Protocols
Carl D. Robinson, M.D. 91

Evaluation Aspects of Genetic Counseling
Robert F. Murray, M.D. 93

The Dimension of Self-Concept in Sickle Cell Counseling
David Satcher, M.D. 98

Discussion 102

Educational Techniques

Naomi Chamberlain
Claire Hurst
Cynthia Kaufman
Thomasina Holmes 109

Current Research

Molecular Basis of Sickling
Ronald Nagel, M.D. 121

The Sickle Cell in the Circulation
John Bertles, M.D. 126

Clinical Studies in Sickle Cell Syndromes
Howard Pearson, M.D. 128

Panel

International Perspectives
Graham Serjeant, M.D. 135
James Bowman, M.D. 143

Discussion 146

Grand Rounds: Adult Case

Presentation of the Adult Case
David Satcher, M.D. 153

The Internist's Perspective
Joanne Smith, M.D. 156

The Hematologist's Perspective
John Bertles, M.D. 158

The Ophthalmologist's Perspective
Maurice F. Rabb, M.D.
Lee M. Jampol, M.D. 160

The Endocrinologist's Perspective
Robert Penny, M.D. 162

Discussion
Louis Sullivan, M.D. -- moderator 166

Panel

Education and Sickle Cell Services as an Integral Part of Comprehensive Health
A. J. Henley -- moderator
Bertram Lubin, M.D.
Eleanor G. Goines
Sylvia Wooten, M.D. 175

Conference Wrap-Up

Harold Ballard, M.D. 187

Appendix

Conference Participants 197

PREFACE

The first National Sickle Cell Educational Symposium was organized to provide an opportunity for health professionals from a variety of backgrounds -- medicine, education, social services -- to share their different perspectives on their research on hemoglobinopathies and their work with sickle cell patients.

I believe that all who attended this meeting felt enriched and enlightened by the conference. It was decided to publish this proceedings of the occasion so that those unable to share the experience could still benefit from it. It is hoped that the reader will emerge from these pages with an improved perception of health education as the foundation for "wellness."

Howard F. Manly, M.A.
National Sickle Cell
Disease Program

INTRODUCTION

The First National Sickle Cell Educational Symposium represented a milestone in the National Sickle Cell Disease Program. A multidisciplinary approach was used to develop the conference theme of "Education Today, Better Health Tomorrow." It was an ambitious undertaking that brought together health workers from a variety of fields -- from scientific investigators, to practicing physicians, community health workers, and educators.

Although united by their interest in a comprehensive approach to sickle cell disease, there are very few opportunities for geneticists, researchers, educators, clinicians, and counselors to interact in the same setting. This symposium provided the occasion for them to share their different perspectives on the same problem.

The conference format was unique. The traditional lecture approach for the presentation of all papers was replaced by a program organized around two "Grand Rounds." One case involved an adult patient with sickle cell disease; the other centered on a pediatric case. Following the presentations of the patients' case histories, and clinical and laboratory findings, specialists in different fields discussed the cases from the perspective of their areas of expertise. A series of four mini-symposia covered topics on clinical management, genetic counseling, educational techniques, and current research. Finally, several formal presentations completed the program.

Hopefully, those who attended the symposium returned to their work setting with a more in-depth appreciation of the clinical management of sickle cell patients, an increased knowledge and understanding of the status of current research, and a broader concept of effective approaches to counseling and education. We firmly believe that the exchange of ideas among members of different health professions, which occurred at this meeting, will contribute to enhancing the quality of life for patients with sickle cell disease.

To make the substance of the meeting available to all those interested in the treatment, care, and research in sickle cell disease, we have published the proceedings of this most fruitful conference.

Clarice D. Reid, M.D.
Coordinator
National Sickle Cell
Disease Program

keynote address

HISTORY OF THE NATIONAL SICKLE CELL PROGRAM

Robert I. Levy, M.D.

I would like to use this occasion to review the history of the National Sickle Cell Program: what it is, where it is, and where we think it is going. Things in Washington have a way of changing all the time. The National Heart and Lung Institute is soon to become the National Heart, Lung, and Blood Institute. Perhaps the best way to begin this address is to begin historically. Many of the events that embody what is now the National Sickle Cell Program are intrinsically involved in the history of the Heart and Lung Institute, and have occurred over the last six years.

The National Heart and Lung Institute and the National Sickle Cell Program

In 1971, in his State of the Union Address, President Nixon spoke about the problem of sickle cell disease and the need for more research and education in this area. In 1972, Congress responded with the National Sickle Cell Anemia Control Act, which called for an increased effort in the areas of education and research. In that same year, within the Institute, the Sickle Cell Disease Branch was established to coordinate the national program.

Another event that is very closely tied to the Sickle Cell Disease Program and has affected its course and direction is the passage by Congress of the National Heart, Blood Vessel, Lung, and Blood Act of 1972. This Act did many things. It established bureau status for the National Heart and Lung Institute. It also greatly increased the mandate of the Institute and resulted in a rather broad reorganization of the way the Institute functions.

The mandate, as set down in the passage of the National Heart, Blood Vessel, Lung, and Blood Act, called not only for the Institute's continued involvement in supporting excellence in basic research; it also called for the Institute to get more heavily involved in clinical trials, testing research results and hypotheses. Furthermore, the Act called for the Institute's involvement in prevention, education, and control programs for physicians, other health professionals, and the public, and in translating research results to the community.

Thus, for the first time, the Institute was responsible for the full biomedical research spectrum: from basic research, through clinical trials and evaluation, to the practical application and translation of research results to the care of the patient in the community. For the first time we became responsible for three different kinds of actions.

We have always been responsible for the acquisition of new and basic information. However, we were not formerly as much involved as we are now in testing basic research facts through clinical trials. We are now also responsible for translation activities and for applying information for better prevention, detection, and treatment of disease.

In 1972, the Heart and Lung Institute was reorganized to approach this new mandate in a functional manner. All of the research efforts were put together in categorical divisions whether they were funded by grants, contracts, or direct support. Thus, all of our work in lung diseases is now emanating from the Division of Lung Diseases. All the work in heart and vascular disease comes out of one division - the Division of Heart and Vascular Diseases, and all of the work in the area of blood diseases and blood resources comes out of one division - the Division of Blood Diseases and Blood Resources.

Organizationally, this is a relatively simplistic structure compared to the organizational structure of the National Sickle Cell Program, in that the National Sickle Cell Program goes well beyond the scope of the National Heart and Lung Institute.

Organizational Structure of the National Sickle Cell Program

With the passage of the Sickle Cell Anemia Act in 1972, responsibilities were given to the Secretary of Health, Education, and Welfare, who in turn delegated the responsibility for the program to the Director of NIH. He delegated the responsibility for the coordination and direction of the national program to the National Heart and Lung Institute, Division of

Blood Diseases and Blood Resources, Sickle Cell Disease Branch. The Branch Chief serves a dual role. This person is responsible for the direct activities of the branch in mission-oriented direct research, targeted research, and education and control programs sponsored directly by the Institute. The Branch Chief is also responsible for coordinating the national program that involves other government agencies and groups, including the Health Services Administration (HSA), the Center for Disease Control (CDC), and their parent organization, the Department of Health, Education, and Welfare (HEW).

The Sickle Cell Disease Program is assisted and overviewed by the Sickle Cell Disease Advisory Committee. The members represent domestic, nonfederal research or educational institutions, and lay members who are qualified to give scholarly advice on the problems in sickle cell disease and opportunities for research.

The National Sickle Cell Disease Program is as broad as the mandate given to us in 1972. It includes basic research, targeted research, educational activities, and screening and counseling clinics. It includes an upgrading of methods for detection and standardization of the detection of hemoglobin abnormalities. It also includes one specific kind of program that probably deserves special note -- the Comprehensive Sickle Cell Centers which, in 15 centers around the country, embody the full spirit of the National Sickle Cell Program.

These Sickle Cell Centers are associated primarily with university centers, but they are mandated to be involved in the community. They are not only required to do basic and clinical research, they must also have educational and demonstration activities. These activities must involve the public, and most specifically, those affected with the disease.

The coordinator of the entire National Sickle Cell Program is also chief of the Sickle Cell Disease Branch. She coordinates the research, education, and demonstration activities. She also coordinates activities within the Heart and Lung Institute with the activities outside of the Institute, as in the HSA Sickle Cell Clinics and the Hemoglobin Proficiency Testing Laboratory at CDC.

All of you may know that the present coordinator is the Chairman of this morning's session, Dr. Reid, who I think is now sentimentally referred to by her staff as the "Big Wheel."

In 1975, our expenditure for sickle cell disease was slightly more than $17 million. This is just slightly more than one third of the budget of the Division of Blood Diseases and Blood Resources. Sickle cell disease is now the major program area in the Division of Blood Diseases and Blood Resources.

The Magnitude of the Problem

It would not be too difficult to justify this expenditure considering only the medical problems associated with sickle cell disease: the crises, the hemolytic anemia, the increased morbidity and mortality. But thinking of sickle cell disease as a public health problem, one can more than justify this expenditure if we consider a few basic facts.

There are over 50,000 Americans with sickle cell anemia and over 2 million Americans, primarily Black, with sickle cell trait. In fact, one out of every 10 Black Americans is estimated to have the trait. Medical care costs are rising rapidly. For sickle cell anemia, it is calculated that the cost right now per patient per year ranges between $2,000 to $15,000.

The total medical care costs for sickle cell anemia in this country today are approximately $500 million annually. This must be paid by the patient, or by his or her family, or through third-party reimbursements.

When one thinks of sickle cell disease and its sociological, economic, and psychological aspects, one realizes this is a national program worth supporting. Besides the problem that the sickle cell patient and his family have in getting health insurance and in avoiding discrimination in job opportunities, the family is also limited by having to take care of a patient with sickle cell disease. Another important consideration is the significant emotional and psychological impact that any chronic disease has on a patient and on a patient's family.

The National Sickle Cell Program

In the National Heart and Lung Institute,

we direct our attention to actions that can be applied now for the better prevention, detection, and treatment of disease. In the Sickle Cell Program, this is primarily done through educational activities. We direct our attention to clinical trials seeking to find ways to prevent or control the sickling process. We also direct our attention to the acquisition of new and better knowledge about the disease and its natural history.

The next speaker will talk about the problems in professional education -- increasing the awareness of the physician of the many different ways that sickle cell anemia may present to the health care professional. We are involved in this type of education, but a much more important educational role we have is to try to dispel the many fantasies and misconceptions that exist concerning sickle cell disease. For example, sickle cell anemia is not a venereal disease.

Sickle cell trait is not a mild form of sickle cell anemia. Sickle cell patients do not have mental retardation, do not necessarily have severe morbidity or mortality that result in a dramatically shortened life span, and are not necessarily invalids. Sickle cell disease extends well beyond the Black population, and sickle cell carriers do not necessarily produce children with sickle cell anemia. All of these misconceptions must be clarified and replaced by facts that more clearly represent the disorder and its problems.

Besides this effort to teach people about what a disease or disorder is and is not, we have been actively involved in clinical trials in sickle cell anemia. We have been somewhat frustrated in our attempts to develop an effective therapy to control or prevent the sickling process. Several leads have been followed but have not borne out with clinical testing. For example, urea has not shown the promise we thought it would. It has not proven efficacious in clinical trials. Cyanate does seem to affect the sickling process, but has been associated with severe neurotoxicity when given orally. However, since it appears to work under certain conditions, we must find better ways to administer this drug. Zinc has been proposed as the new drug to treat the process. We really have no good information from any well-controlled clinical trials that zinc has any promise. We have a number of other drugs or agents that may be effective in controlling the sickling process, but up to this point we have no hard evidence that any of these agents work effectively in man.

What We Know

The acquisition of knowledge is the area we know best at the National Institutes of Health. We have a good deal of information and a large number of basic facts about sickle cell disease. In contrast to what we know about so many other disorders, we know the basic molecular defect in sickle cell disease. We know that the beta chain of hemoglobin in a subject with sickle cell anemia is wrong in one single amino acid. The replacement of a valine for glutamic acid at position six results in all of the abnormalities that we come to think of as sickle cell anemia.

We know that sickle cell anemia is a genetic disease. We know it is transmitted as a simple autosomal recessive trait. Knowing this, we know that for a child to be born with sickle cell anemia, both mother and father must have the trait. Using simple Mendelian genetics, only one in four children will be affected when both parents have the trait.

We know that sickle cell hemoglobin, when deoxygenated, is very susceptible to aggregation and to solubility changes, which result in the sickled red cell. The clumping of the cells in the peripheral capillaries and arterials results in decreased blood supply to the tissue and microinfarctions.

We now have very effective and sensitive diagnostic methods to diagnose the hemoglobin abnormality we call sickle cell disease and other hemoglobin abnormalities. We also know the sickle cell patient is more susceptible to infections caused by the pneumococcus and salmonella bacteria, especially during the first two decades of life. However, one could put what we know in a thimble and still have a large amount of space left over for what we still do not know.

What We Do Not Know

We do not know or fully understand the stereochemical changes that are involved in the aggregation and formation of the sickle cell tactoids. We do not know the nature of the equilibrium of the kinetic processes that

are involved in the gel formation. If and when we know this, we can devise better forms of therapies that might prevent the cell from sickling or control a cell that is sickling.

Much of our information about the natural history of sickle cell disease is anecdotal. We need better, more sophisticated, more systematic studies of the natural history of sickle cell anemia. We have no way of measuring or understanding what occurs in the tissues with the formation of sickle cell microinfarcts. We do not know why crises occur in some subjects at some points in time and not in others. We do not understand why sickle cell anemia can manifest itself so much more severely in some people than in others.

It has been suggested that the immune mechanisms in the patient with sickle cell anemia may be altered. Studies thus far have not detected any basic problems in the immune system. The problem seems to be in the environment and probably lies with the microinfarctions that occur in so many tissues.

We need to know better ways to control the sickling process. We need to better understand the factors that affect the morphology of the sickle cell, that affect its viscosity. We need to better understand the basic mechanisms of hemoglobin synthesis. We know that the infant with sickle cell anemia is relatively protected in the first six months of life when fetal hemoglobin is present. If we understood the switch mechanism by which fetal hemoglobin is replaced by adult hemoglobin in early life, then perhaps we could redirect the mechanism and increase the amount of fetal hemoglobin that would be protective to the sickle cell patient.

These are just some of the things that we do not know or would like to know if we are truly to control this disorder.

The Future

I have talked about the National Sickle Cell Disease Program's commitment to activities and actions in three areas; we will stand committed to these three areas over the next several years. I would emphasize, however, that since we still cannot prevent or control the sickling process most of our therapy for sickle cell disease is palliative. Our major effort in the next three to five years will be in more and better research. It is our firm conviction that more research today holds the only true promise to control of sickle cell disease tomorrow.

formal presentation

SICKLE CELL ANEMIA: "THE GREAT MASQUERADER"

Helen Ranney, M.D.

The attention given to sickle cell anemia in the last five years has lead to significant advances in our understanding of the disease and also to significant, if less widely recognized, improvements in its management. This symposium will deal in greater depth with the educational aspects of the programs in sickle cell disease. Education may be broadly defined to include the advances made in our comprehension of the pathogenesis of the disease and in experimental approaches to therapy.

The curious shape of the sickle cell was first observed in Chicago by Herrick about 65 years ago. The dependence of the phenomenon of sickling on deoxygenation of the hemoglobin was not appreciated for more than ten years after his initial observation. By the 1930's it was recognized that sickling could be demonstrated following the deoxygenation of the red cells in many healthy, asymptomatic individuals, as well as in patients who had no other obvious cause for a severe hemolytic anemia or for the unexplained recurrent painful crises that were ascribed to occlusion of vessels by sickled cells. Sickling was known to be more common in individuals of African ancestry, but its prevalence in those groups was not known. Sickle cell anemia was occasionally found in other groups, particularly in Americans of Greek or Italian ancestry.

When I was a medical student, sickle cell anemia was attributed to a disorder of the red cell stroma, and the hemolytic anemia was attributed to some ill-understood defect in the stroma that caused this curious shape of the cells. It was not until the late 1940's that an abnormal hemoglobin was found in cells which were susceptible to sickling. Following a train ride during which Castle and Pauling discussed sickling, Pauling, with his collaborators, Itano and Singer, found that the hemoglobin of individuals with sickle cell anemia differed electrophoretically from normal hemoglobin, and that the hemoglobin of individuals with the asymptomatic, nonanemic sickle cell trait, was a mixture of hemoglobin S or sickle hemoglobin and normal hemoglobin A.

A little earlier, Neel, Beet, and a little-known Brazilian hematologist had collected formal genetic evidence from family studies that corroborated the advances in biochemical genetics. In genetic studies sickle cell anemia represented the homozygous state for a genetic factor that was manifest in the heterozygous state as sickle cell trait. The demonstration that hemoglobin S was electrophoretically different did not, of course, explain its solubility properties.

There are now over 100 different hemoglobin variants that have the electrophoretic mobility of hemoglobin S, but only the hemoglobins that have the specific amino acid substitution of hemoglobin S undergo polymerization of deoxygenation. There is general agreement that sickling described in association with other abnormal hemoglobins has been the result of artifacts, and that true deoxygenation-dependent sickling occurs only in the presence of the valine for glutamic acid substitution of hemoglobin S.

In 1950 John Harris demonstrated that deoxygenated concentrated solutions of sickle cell hemoglobin exhibited decreased solubility and formed liquid crystals or tactoids. Figure 1 shows a sickle cell preparation and a microphotograph of a deoxygenated solution of hemoglobin S at high concentration, 15 grams percent, that contains aggregates of hemoglobin S. The formation of these sickle aggregates or polymers on deoxygenation dictated the sickled shape of the red cell when the ligand was removed from the hemoglobin. The subunit composition of hemoglobin was not known until the 1950's when the tetrameric two pair of unlike chains, the alpha and non-alpha polypeptide chains, were established by the work done in several laboratories, particularly by Schroeder, Field, and Vinograd. In 1954 Ingram showed that a single peptide in hemoglobin S differed from the same corresponding peptide of A and subsequently demonstrated the substitution of valine for glutamic acid at the sixth position of the beta polypeptide chains in hemoglobin S. The initial examples of what would eventually be a large number of abnormal hemoglobins were then described, and

hemoglobin S and C were shown to result from the simultaneous presence of allelomorphic genes.

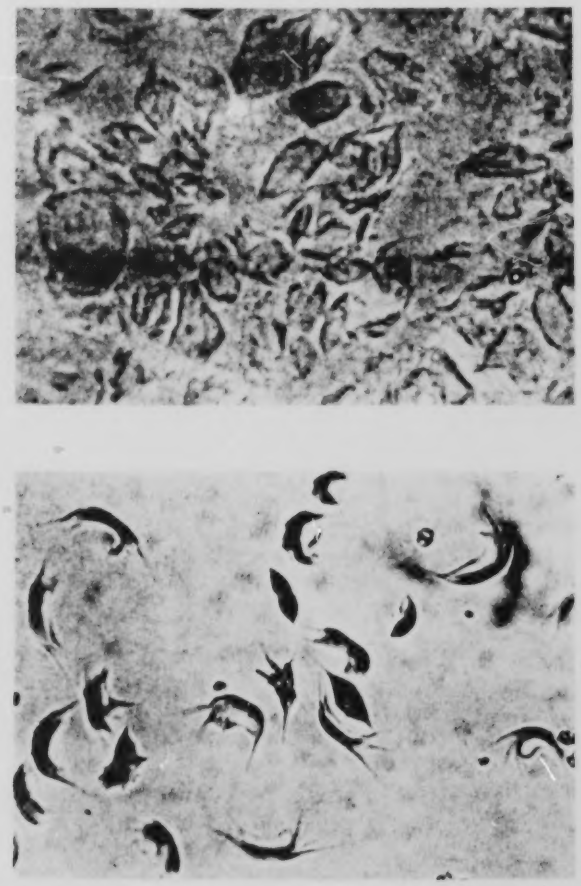


Figure 1. A sickle cell preparation (top) and a microphotograph (bottom) of a deoxygenated solution of hemoglobin S at high concentration, 15 gram percent, that contains aggregates of hemoglobin S.

The work of Perutz and his associates in several laboratories has provided a large body of knowledge about the structure of hemoglobin. They have used x-ray crystallography to establish the structure of normal hemoglobin, of hemoglobin variants, and of different leganded forms of hemoglobin, together with delineation of the amino acid sequence of hemoglobin.

In 1957 Allison suggested that the prevalence of sickle cell trait in tropical Africa had been maintained by selective protection of sickle cell trait individuals over normal subjects in infections with falciparum malaria. Thus, it was nearly 20 years after the recognition of hemoglobin S before an explanation of the high incidence of sickle trait in Africa was accepted. Luzzatto has more recently shown that sickle red cells containing falciparum parasites become rigid and are probably destroyed before the malaria parasites have multiplied.

The impairment of sickling in the presence of another hemoglobin was demonstrated by Karl Singer for hemoglobin F. He also noted that aggregation of hemoglobin S, impaired by hemoglobin F, was favored by hemoglobin C. Thus, the presence of hemoglobin F seemed to decrease, and the presence of hemoglobin C to increase the insolubility of S hemoglobin when the properties of a mixture of S and F, or S and C, were compared with mixtures of S and A.

Studies of impairment of sickling in the presence of other hemoglobins were later extended by observations on hemoglobin C, in which sickling was impaired by the presence of a second amino acid substitution in the beta chain of an individual who also had the valine for glutamic substitution of hemoglobin S. The double amino acid substitution yielded a sickling hemoglobin with electrophoretic mobility resembling hemoglobin S.

At the present time, as Dr. Levy mentioned, three areas for basic research on sickling seem particularly promising:

- molecular structure and kinetics of formation of the fibers of deoxygenated hemoglobin S.
- kinetics of polymer formation that would determine the speed of sickling.
- the role of the microvasculature.

First, the molecular structure and kinetics of formation of the fibers of deoxygenated hemoglobin S are obviously important in sickling. Two approaches have been used for studies of the structures of the fibers of deoxygenated hemoglobin S: 1) electron microscopy and/or

x-ray diffraction; and 2) the interactions of hemoglobin S with other abnormal hemoglobins to ascertain the effects of sickling properties of changes in specific sites on the different polypeptide chains. In Figure 2 the fibers of hemoglobin S in the cytoplasm of the deoxygenated sickle cell are shown. These tiny fibers, shown cut on end in top of the figure and in parallel in the bottom of the figure, represent the structure at higher magnification of the fibers of the liquid crystals or tactoids of Figure 1.

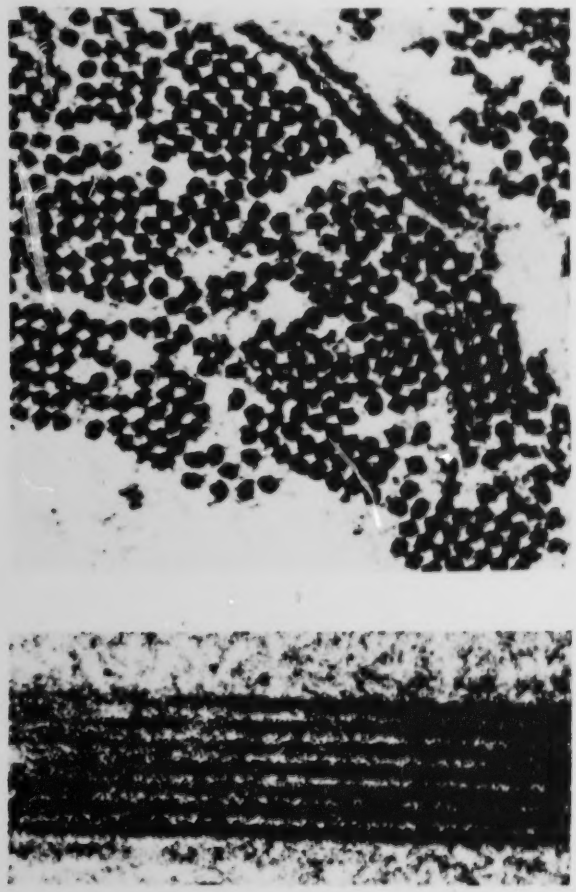


Figure 2. Fibers of hemoglobin S in the cytoplasm of the deoxygenated sickle cell, shown cut on end (top) and in parallel (bottom).

Various models have been constructed to indicate the molecular sites of the observed interactions of the hemoglobin molecules in these fibers. Figure 3 from Hofrichter is a model in which each of the potato-shaped structures represents a tetrameric hemoglobin molecule. Each of the two beta chains in sickle hemoglobin contains a beta-6 valine substitution. The sites of the intermolecular interactions indicate one beta-6 substitution, interacting with a complementary site on an adjacent hemoglobin molecule. The other beta-6 of hemoglobin S may not be involved in an intermolecular context.

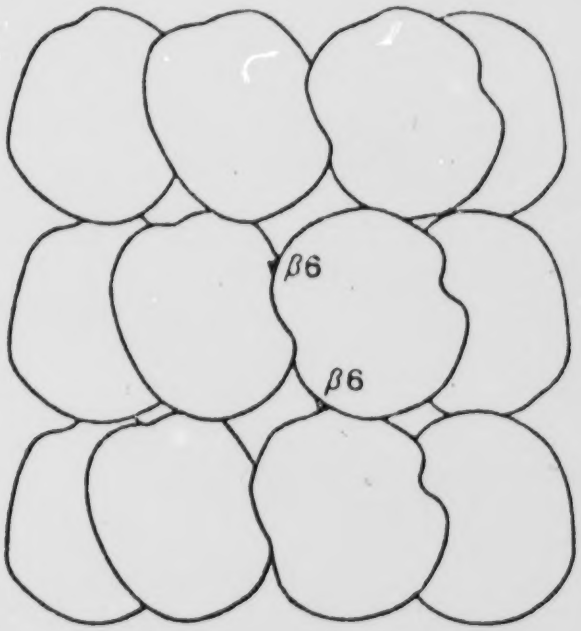


Figure 3. Hofrichter's model, in which each potato-shaped structure represents a tetrameric hemoglobin molecule.

Figure 4, modified by Nagel and Bookchin from Dickerson's model of hemoglobin, indicates the sites of substitutions which modify sickling, as deduced from observations on the interactions of hemoglobin S with other abnormal hemoglobins. One such abnormal hemoglobin, hemoglobin Memphis, has an amino acid substitution at alpha 23; hemoglobin C (Harlem) and hemoglobin Korle-Bu have substitutions at beta 73. The site of substitution for both hemoglobin O (Arab) and hemoglobin D (Punjab), both of which promote the aggregation of hemoglobin S, is at beta 121.

Figure 4. Dickerson's model of hemoglobin, as modified by Nagel and Bookchin, indicating the sites of substitutions that modify sickling.

The amino acid substitutions that favor sickling are apparently silent in the heterozygous state (with hemoglobin A), but will result in symptomatic sickle cell disease when present with a single gene for hemoglobin S. Thus, hemoglobin S/C, S/D, and S/O disease account for many cases of sickle cell disease of mild to moderate severity.

Returning to model building, Figure 5 shows the sites postulated by Wishner and his colleagues, who studied crystals of hemoglobin S. This model accounts for the different intermolecular interactions described for the interacting hemoglobins noted by Bookchin and Nagel. While the molecular arrangements of the sickle polymer are themselves important, the kinetics of polymer formation that would determine the speed of sickling constitute another important investigative area. Evidence from Eaton's laboratory suggests an enormous dependence of those kinetics on concentration of hemoglobin S.

In blood smears of individuals with sickle cell disease, sickled red cells are frequently encountered. Obviously, those cells are not sickled because of a lack of oxygen. Studies of these irreversibly sickled cells were carried out by Dr. Bertles, who showed some years ago that a population of irreversibly sickled cells contained smaller proportions of hemoglobin F than did the remainder of the red cells. Such irreversibly sickled cells have a survival time even shorter than that of the average cell population in sickle cell anemia.

Do irreversibly sickled cells result from repeated sickle-unsickle cycles? There is an increase in viscosity in the cell as the hemoglobin S polymerizes to form the fibers shown in Figure 2. And these projections of red cell membrane containing a small amount of hemoglobin may be seen in scanning electron microscopy, as shown in Figure 6. As the sickled cells round up on oxygenation they may lose these projections, breaking off a projection which has a larger proportion of membrane than of hemoglobin. As a consequence, the cell is repeatedly damaged by the sickle-unsickle cycles. Some cells assume a sickle shape that is not reversed even on exposure to 100 percent oxygen.

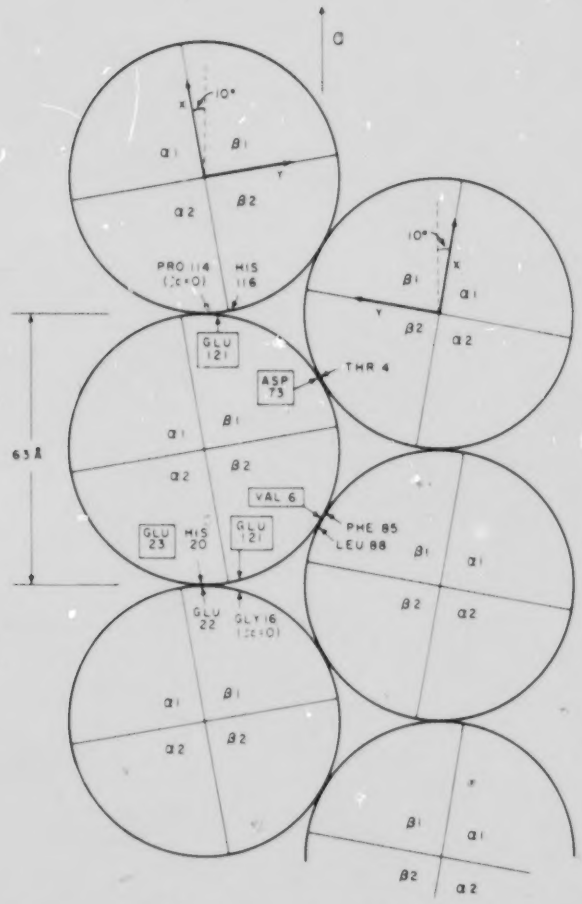


Figure 5. Wishner's model of hemoglobin based on his studies of crystals of hemoglobin S.

Is there a membrane interaction in sickling? The red cell membrane usually assumes a shape that is dictated by the physical state of hemoglobin S, but in irreversibly sickled cells there is a possibility that permanent membrane damage has followed sickling, perhaps repeated cycles of sickling. The accumulation of calcium in membranes of sickle cells and the much increased rigidity of sickled cells play an important role in the aggregation of sickle cells within the microcirculation.

An area of basic research, which is not clearly defined in research approaches, is the role of the microvasculature. Why, for example, is coronary artery occlusion almost unknown in sickle cell disease? This is usually attributed to the rapidity of flow in sickling, but is that a sufficient explanation? Is there some diffusible metabolic product in different sites in the body that may tend to favor sickling at certain sites? Why do some patients with sickle cell disease have the unfortunate complication of occlusion of neurological vessels, while other patients with sickle cell disease have relatively few evidences of occlusion of vessels, or have their principal manifestations as arthritis or pleurisy, chest disease, or abdominal pain? Do the sites of organ damage in individual patients with sickle cell disease simply reflect different anatomic distribution of the small vessels, or do they reflect metabolic differences in different organs?

Figure 6. Sickled cell showing projections of red cell membrane containing a small amount of hemoglobin.

In the clinical areas in which changes have occurred in sickle cell disease in the last decade, much of the progress is based upon studies of sickle cell disease that have been carried out at various centers. The role of infection in the morbidity and mortality of sickle cell disease has received appropriate attention. I have chosen three among the several studies of infections that have been published: Dr. Barrett-Connor's, Dr. Powars', and Dr. Margaret Robinson's. From studies in all three

centers, it is clear that patients with sickle cell anemia have a greatly increased susceptibility to infection, particularly to pneumococcal infections, during the first five years of life. This occurs during the time when the patients are undergoing autosplenectomy, and the increased susceptibility to infection is reminiscent of the susceptibility to infections of children who have had splenectomies for hematologic disorders other than sickle cell disease.

Dr. Barrett-Connor's study, carried out in Florida, provides clear data about the number of patients who died with sickle cell anemia at a young age, and the association of H-influenza and pneumococcal infections with mortality. Dr. Powars' study from Los Angeles also shows the association of severe fatal infections with pneumococcal infections. The ominous nature of cerebrovascular complications was pointed out in Dr. Powars' and in other studies. The causes of death in sickle hemoglobinopathy in Dr. Robinson's study again shows the ages of death from sepsis, which resemble those seen in the other studies. Mortality in children with sickle cell or S-thalassemia disease is uncommon.

The associated splenic manifestations have also been much more appreciated in adult medicine in recent years, although Dr. Pearson and other pediatric hematologists recognized splenic sequestration in young children many years ago. The rapid development of an enlarged spleen with shock and anemia in young children is called a splenic sequestration crisis, and a similar event may occur in adults with the genetic variants of sickling as in young children with sickle cell anemia. While the acute problem is reversed by prompt transfusion, there is a tendency for recurrence. Many sequestration crises occur in young children and during the ensuing years the spleen may become infarcted and fibrotic. In children the threat of repeated crises may be less than in older children or young adults who have persisting splenomegaly. The anemic aplastic crises are among the commonest causes of hospital admission of patients with sickle cell disease. Patients who have sickle cell disease (or other diseases with shortened red cell life span) may become more anemic in the face of infections.

The masquerade of sickle cell anemia obviously affects a great many different specialties in medicine. The young child who presents with the hand-foot syndrome has an orthopedic syndrome suggestive of osteomyelitis. A severe crisis may occur in pregnancy in a patient with sickle cell anemia or a genetic variant, who has been quite well prior to the pregnancy. Chest symptoms, infections, and/or thrombosis in situ in pregnancy frequently present difficult diagnostic problems. Since infection may be followed by occlusion of the microvasculature and microinfarction and since, with thrombosis in situ, secondary infection might occur in infarcted areas, the etiologic distinction between infection and thrombosis may, under some circumstances, be academic.

Unrecognized sickling in pregnancy, particularly the genetic variants, used to be encountered frequently in patients who presented with pleurisy in pregnancy as their first serious complication of sickling. It is now unusual, despite the many different symptoms that sicklers may exhibit, to see patients with sickle cell disease in whom the diagnosis has not been made by the age of 20. This reflects an increasing appreciation of the existence of sickle cell disease, as well as the increasing use of the laboratory in the diagnosis of anemias.

A few patients have progressive renal disease in association with sickle cell anemia. There have been some recent studies to suggest an immunologic basis for this complication, at least in some patients. Another group of uncommon complications that is difficult to understand is the episodes of severe cholestatic jaundice, which may resemble biliary obstruction. The jaundice usually subsides over the course of weeks, and appears to represent some kind of hepatitis with pigment retention. Most of the complications of sickle cell disease, protean as they are, are recognized as manifestations of the disease. Now they occur in patients in whom the diagnosis of sickling has already been established.

In conclusion, I would like to comment on the prevention of sickle cell disease by genetic counseling. I believe that there is general agreement that the aim of genetic counseling is to inform individuals with sickling about the transmission of the gene, rather than the prevention of sickling. Counseling of individuals with sickling includes more than just genetic counseling; it implies the conveyance of medical information about the nature of sickle cell trait and of sickle cell disease, including the genetic aspects, to the individual who has the trait or the disease.

A second approach to the prevention of sickle cell disease has been through antenatal diagnosis, which is now possible for sickle cell disease. Here, more research must be done. The diseases in which antenatal diagnosis has had wide use have been those in which antenatal diagnosis could be made using amniotic fluid. In contrast, antenatal diagnosis of sickle cell anemia requires that fetal blood be studied. The techniques of obtaining fetal blood will require significant improvement before antenatal diagnosis can be recommended as a benign procedure for study of the disorders of hemoglobin synthesis of structure.

Over the last 20 years, a great many advances have been made in our knowledge of hemoglobin and of sickling. Our concepts of the nature of sickling, of its effect on the red cell, of the effect of sickling red cells on the circulation, and of the circulatory changes on organ function continue to change. The hope for better treatment and better management of sickle cell disease finds promise in the dramatic advances that have been made in our understanding of sickling in the last two decades.

grand rounds: pediatric case

PRESENTATION OF THE PEDIATRIC CASE

Marilyn H. Gaston, M.D.

Our pediatric case involves J.W., now 16 years old, who was the third child of a 28-year-old mother. The mother's previous children, aged 6 and 3, were normal. There was no history of blood disease in the family, but the mother was told in the third trimester of pregnancy that she had sickle cell trait. No tests were done on the father.

The child was born at term with a birth weight of 7 pounds, 5 ounces. The initial Apgar score was 8. Neonatal course was uneventful and the child was discharged on the third day of life.

He did well at first but, beginning at six months of age, the mother thought that he was more irritable and fussy than her previous children had been. At the sixth month well-child visit, the spleen was noted to be palpable 2 centimeters below the left costal margin.

At 8½ months of age, the patient became very irritable. Painful swelling on the backs of both hands was noted. He was taken to the emergency room and then admitted to the hospital with a temperature of 101 F.

X-rays of the hands revealed only soft tissue swelling. Laboratory data on that admission is summarized in the table below.

Table 1. Laboratory Data, Pediatric Case

- Hemoglobin - 6.9 gm/dl
- White Blood Cells - 18,500/mm

Polys	=	65%
Monos	=	5%
Bands	=	10%
Lymphs	=	20%

- Reticulocytes = 9.2%

Figure 7. At 8½ months of age, the patient became very irritable. Painful swelling on the backs of both hands was noted.

Red blood cell morphology revealed a rare sickle cell with moderate targeting and polychromasia. Hemoglobin electrophoresis showed SS with some fetal and fetal Hb determination by alkali denaturation was 12.8 percent.

Because of fever and pain, a diagnosis of osteomyelitis was entertained. After blood cultures were taken, therapy with intravenous oxicillin was started. Within 12 hours the child became afebrile, and at 48 hours the blood cultures showed no growth. Antibiotic therapy was stopped and the patient was discharged from the hospital. Edema of the hands persisted for about one week after discharge.

Figure 8. X-rays of the hands taken two weeks following the patient's discharge from the hospital revealed multiple osteolytic lesions of the metacarpals and phalanges.

After two weeks, hand x-rays were repeated and showed multiple osteolytic lesions of the metacarpals and phalanges. At this time the child's hands clinically appeared normal and were not painful.

During the next year the child had multiple episodes of painful swelling of the hands and feet. The mother purchased two kinds of shoes - one was a canvas pair for occasions when his feet were swollen and painful, and a regular pair of shoes for other times.

Despite a fair appetite, the child's growth was less than optimal, paralleling the third percentile for height and weight.

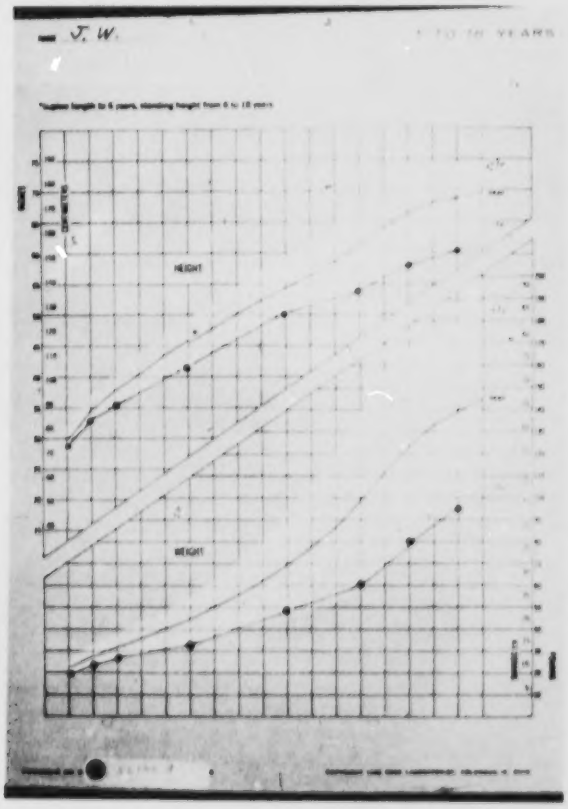


Figure 9. Height and weight chart for J.W.

The child did fairly well during the next few years. On numerous occasions he complained of feeling bad with nonspecific pain, but he did not require hospitalization. A recurrent problem

was enuresis. A urological workup was done, including an intravenous pyelogram, and was negative.

At the age of six years the child developed severe, painful swelling of the left elbow and the right knee. He was admitted to the hospital for evaluation. Laboratory data at that time revealed a hemoglobin of 6.9 grams; hematocrit was 21 percent with a white blood count of 19,600; bands, 8; polys, 56; lymphs, 30; and monos, 6.

The blood smear showed many sickled cells, moderate targeting, and occasional nucleated red cells. The sedimentation rate was 12 millimeters per hour. The patient appeared toxic and was complaining bitterly of pain. The heart was enlarged with the PMI 3 centimeters outside the midclavicular line, with a rate 120 per minute. The rate was regular.

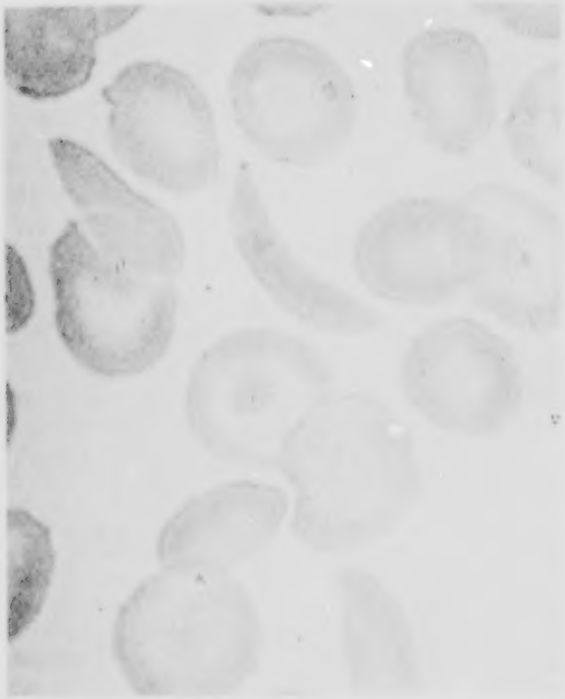


Figure 10. Blood smear showing sickled cells.

A grade 3 out of 6 systolic ejection murmur was heard along the left sternal border. There was also an early low-pitched rumbling diastolic murmur heard at the apex but it did not radiate. The chest x-ray showed generalized cardiomegaly affecting all cardiac chambers. The vascularity of the lung fields was generally increased.

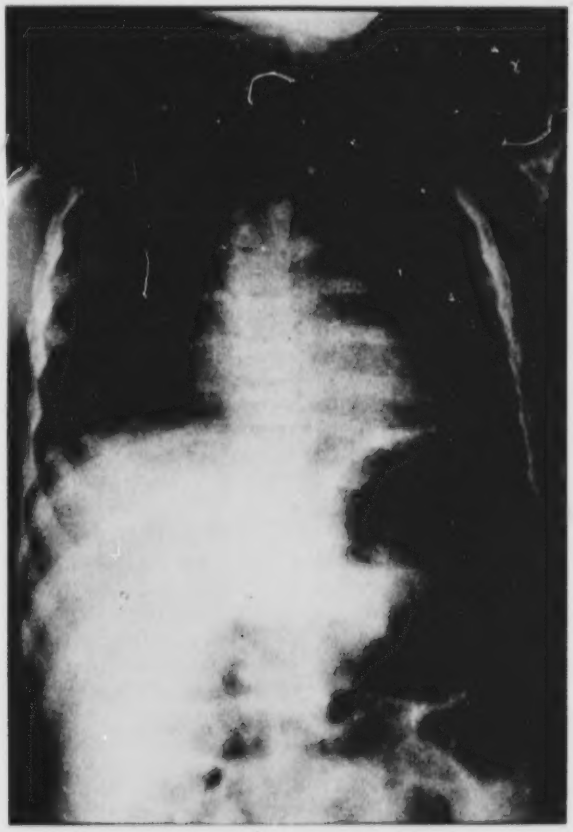


Figure 11. Chest x-ray revealed generalized cardiomegaly.

The EKG revealed sinus tachycardia with a PR interval that was prolonged at .22 seconds, and also left ventricular hypertrophy. A throat culture revealed only normal flora. The patient was treated with intravenous fluids and Tylenol. When he was afebrile, the murmurs were much softer in intensity.

During each of the next five years, he had three to four episodes of pain in his abdomen or in his extremities. Each episode was of sufficient severity to prevent school attendance.

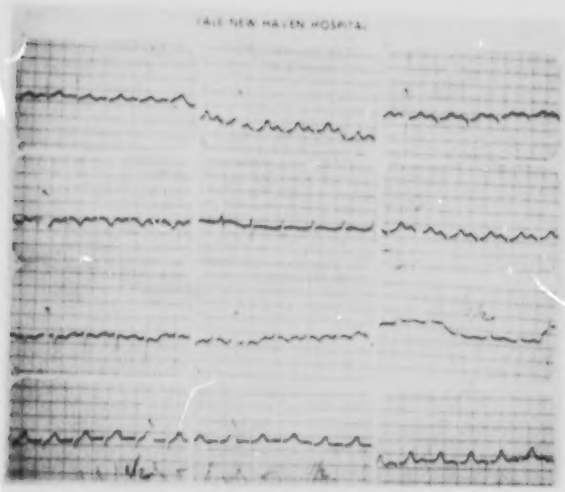


Figure 12. Electrocardiogram taken of the patient at six years of age.

He was hospitalized about once a year for severe pain that persisted more than 36 hours. Therapy on these occasions included IV fluids, oxygen, antibiotics, and analgesics. His school attendance was erratic. Despite tests which indicated above average intelligence, school performance was marginal. His teachers described him as withdrawn and difficult to reach. He had emotional problems associated with small stature and delayed maturation. He subsequently dropped out of school at 16 years of age, and has been unable to find regular employment.

THE GENETICIST'S PERSPECTIVE

Robert F. Murray, M.D.

Sixteen years ago when J.W. was born the average physician had little or no knowledge of the genetic aspects of sickle cell anemia, even though the mode of inheritance had been described ten years earlier by Neel and Beet. Well-trained hematologists were aware of the mode of inheritance of this condition, but most did not do routine testing or family counseling for sickle cell anemia. Counseling that was done at that time was probably inadequate.

This lack of knowledge concerning sickle cell disease is all the more surprising since the specific amino acid abnormality responsible for the defect in sickle cell hemoglobin had already been identified by Ingram. And although medical genetics was beginning to be accepted as a valid "subspeciality," genetic principles were not being applied in patient care. This attitude toward genetics and medical genetics continues to persist to some degree today.

Recently a survey of the genetic knowledge and attitudes of a random sampling of physicians with boards in family practice, pediatrics, or Ob/Gyn, was carried out under the auspices of the Committee for the Study of Inborn Errors of Metabolism. Among other things, it showed:

(1) That 96 percent of physicians who responded felt it was important to detect potential or actual genetic disorders.

(2) That 73.5 percent of physicians felt that genetic screening for particular traits or conditions should be encouraged.

But the survey also revealed:

(3) That most physicians had little or no formal training in genetics or genetic counseling, and only half, who had been practicing for less than six years, had had courses in genetics.

(4) That only 27 percent of physicians felt their own genetic counseling was effective.

(5) That only 27 percent felt that screening for sickle cell trait over the past few years had been beneficial.

The general lack of background information in genetics by practitioners 16 years ago, and by even the well-trained medical specialists of today, is reflected in the paucity of genetic information recorded in J.W.'s case and in the way that information is provided.

The only reference to the genetic aspects of the case was in the statement, "There was no history of blood disease in the family, but the woman was told in the third trimester of pregnancy that she had sickle cell trait. No tests were done on the father."

Considering the general attitude of physicians toward genetics and genetic counseling at the time this child was born, it is indeed remarkable that a sickle cell test was even done at all.

Figure 13. Criteria for Autosomal Recessive Inheritance

1. The trait characteristically appears only in sibs, not in their parents, offspring, or other relatives.

2. On the average, one-fourth of the sibs of the propositus are affected; in other words, the recurrence risk is one in four for each birth.

3. The parents of the affected child may be consanguineous.

4. Males and females are equally likely to be affected.

As Figure 13 indicates, sickle cell anemia is inherited as an autosomal recessive trait. This type of inheritance is characterized by the fact that affected individuals usually occur in a single generation and not only have unaffected parents, but usually have a family history or pedigree that is unremarkable.

Figures 14 and 15 depict the typical pedigree of an autosomal recessive disorder. The condition only appears in brothers and/or sisters but not in their children, parents, or other relatives. There is usually no sex preference; that is, male and female offspring of couples at risk are affected with equal frequency.

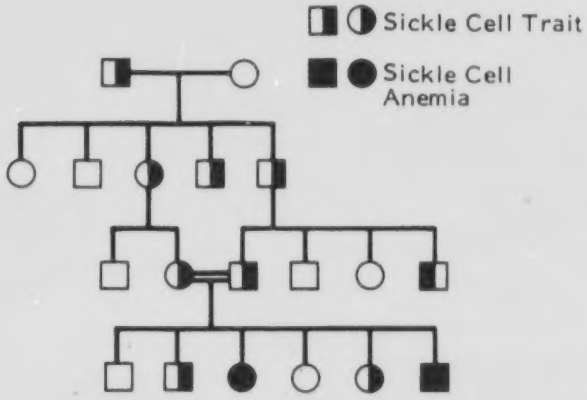


Figure 14. Pedigree of a kindred with sickle cell anemia showing that dominance and recessiveness are characteristics of the phenotype, not of the gene.

The findings in families with sickle cell anemia are consistent with the pattern shown in Figure 15. Although it is uncommon in U.S. populations, mating between genetically related persons, as shown above, will increase the likelihood that an autosomal recessive trait will occur since mother and father have common ancestors and, therefore, have an increased chance of both carrying the same mutant gene.

Marriage between genetically related persons does not generally contribute to the frequency of a disease when carriers are relatively frequent, as with the sickle cell gene in the Black population, where approximately 1 in 12 individuals is a carrier. Mating between relatives might be a factor in the U.S. population where the carrier frequency of the sickle cell gene is roughly estimated in some studies to be about 1 in 500.

When both parents are carriers of the sickle cell gene mutation, each offspring will have a 1 in 4 or 25 percent chance of having sickle cell anemia. The mechanism of inheritance of autosomal recessive traits is shown on Figures 14 and 15. We see the mechanism of inheritance and the way that the recurrence risk is determined for sickle cell anemia.

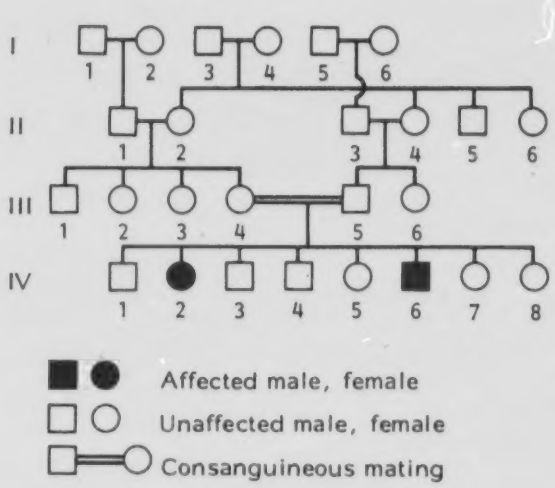


Figure 15. Pedigree pattern of an autosomal recessive trait.

Before screening programs were established virtually 100 percent of couples at risk, that is, both parents are carriers of the sickle cell gene, were recognized, as in the case of J.W., only after the diagnosis of sickle cell anemia was made in one of their children. The parents of J.W. might have been detected earlier as an at-risk couple but the test was not done until the third trimester of pregnancy.

If a genetic workup is to be performed during pregnancy, it must be done within 16 weeks, preferably as early as 10 to 12 weeks, and it must involve both husband and wife. True, if the woman's test is negative, she need not worry about having a child with sickle cell disease, but if she is one of the approximately 1 in 10 Blacks in this country who carries the sickle cell gene, the father must be tested to determine whether or not the parents are one of the 1 in 100 couples at a one in four risk of having a child with a hemoglobinopathy. This will ensure the most accurate genetic counseling.

Prenatal diagnosis of hemoglobinopathies involves taking blood from a placental vessel under direct visualization or blindly, using ultrasound, to follow the point of the needle to try to determine whether or not there is any

measurable production of the usual hemoglobin A-like beta chain in fetal red blood cells. In the past two years, there have been reports of the successful diagnosis of sickle cell anemia, homozygous beta-thalassemia, and homozygous alpha-thalassemia in second trimester fetuses.

Figure 16 is from the recent article by Kan and colleagues, showing radioactive uptake indicating synthesis of beta polypeptide chains of hemoglobin in fetal red blood cells. It shows a small peak of activity where the beta-S chain would be produced, but no peak of radioactive uptake where the beta-A chain is shown on the chromatography. This indicates either that no beta-A chains or insignificant amounts of beta-A chains are being synthesized, suggesting to these investigators that the fetus would indeed have sickle cell anemia; that is, a situation where no essentially normal adult beta polypeptide chains are being synthesized. This diagnosis was confirmed on the red blood cells obtained from the fetus following the termination of the pregnancy.

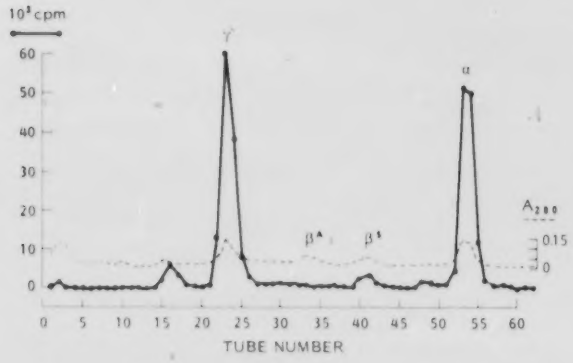


Figure 16. Chromatography of Placental Blood. The sample contained 75 percent fetal red blood cells, and 3.8 mg of hemoglobin was applied to the column. The absorbence at 280 nm included β^A and β^S chains from the maternal blood.

In one recently described case in the New England Journal of Medicine immediately following the article by Kan, the isotopic labeling method usually employed could not be used in a confirmatory diagnostic study following a therapeutic abortion after the presumptive intrauterine diagnosis of sickle cell anemia had been made.

Figure 17 shows the report from the second group showing a similar pattern of synthesis of beta-S, with the solid line showing no beta-A polypeptide synthesis. This study was further complicated by the presence of the hemoglobin G (Philadelphia), which is also present in the fetus and in one of the parents.

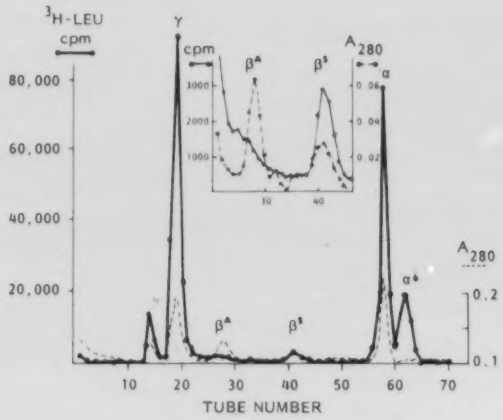


Figure 17. Radiochromatogram of ^{3}H-Leucine-Labeled Fetal Blood. Carrier protein consisted of a mixture of 5 mg of newborn and 5 mg of sickle-trait blood. Insert shows the β^A and β^S regions in more detail. • -- • denotes counts per minute, and o --- o absorbence at 280 nm.

Figure 18 shows the electrophoresis of the blood taken from the fetus following the termination of pregnancy. (For unknown reasons the radioactive labeling experiment was unsuccessful.) This electrophoresis showed the presence of a very small amount of a hemoglobin that migrated like hemoglobin A, suggesting that this child might have had either a diagnosis of S-beta-thalassemia or that it might have had sickle cell trait which could not positively be ruled out. However, the parents decided to terminate the pregnancy even though it might have had the much milder sickle cell disease or it might possibly not have had sickle cell disease after all.

Parents should think very carefully before choosing among the various reproductive options.

The sickle cell diseases, although chronic, expensive, and painful, usually do not produce a helpless, deformed, or retarded person. The prognosis for a given patient cannot be predicted as reliably as it can be for many of the genetic diseases where prenatal diagnosis has been used more extensively.

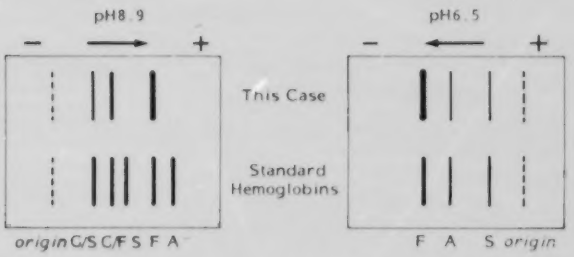


Figure 18. Diagram of Electrophoretic Patterns of Standard Hemoglobins and of Case Presented. Note that at pH 8.9, a small amount of Hb S would be lost in the cathodal trail of Hb F, and no band was seen in this case. Hbs G and S are indistinguishable at pH 8.9. (Left = starch, pH 8.9, and right = citrate agar, pH 6.5.)

Genetic counseling can be a vital adjunct in cases like that of J.W.'s and others, but should include at least accurate laboratory diagnosis, with testing performed only on couples who understand the implications of the test and its limitations before it is performed. When the mother alone requests testing, she must fully understand the implications and the fact that inadequate or inaccurate genetic counseling may be given if the father cannot be tested.

Where the pregnant female is concerned, testing must be carried out early enough, ideally before 12 weeks, so that the couple will be able to exercise all available reproductive options. Except where anemia has been found, there is little justification for routine hemoglobinopathy screening in obstetric clinics or for testing after 20 weeks of gestation, except for clinical management of the pregnant patient.

With all counseling, an attempt should be made to construct a pedigree containing at least the nuclear family and, if possible, three generations including first cousins. Figure 19 lists the minimum information needed for a pedigree that would give you adequate information for genetic counseling. It is certainly important to get information on the nuclear family and, if possible, first-degree relatives because these persons may be carriers of a sickle cell gene or hemoglobinopathy gene, and deserve to have that information.

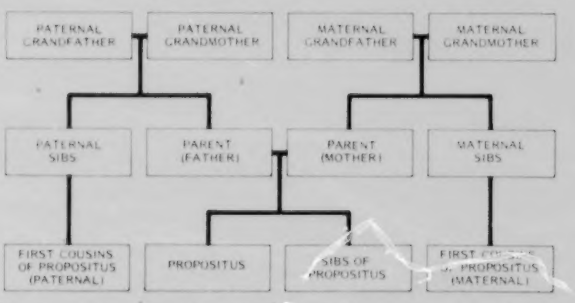


Figure 19. Outline showing the minimum information required for an adequate pedigree for genetic analysis.

The risk of having an affected child increases from 1 in 576 to 1 in 48, depending on whether the person is known to be a carrier of a sickle cell or hemoglobinopathy gene in a population at high risk. In a genetically determined disorder, one must think in terms of couples and/or families, not individuals.

One could argue that this at-risk couple might have been identified if the normal children had been tested for carrier status of a hemoglobinopathy gene since each had a 50 percent chance of being a carrier. There are at least two problems with this approach.

First, there is a 1 in 4 chance in each of these normal children that they might not have carried the sickle cell gene, even though both parents were carriers; and a 1 in 16 chance that both children would not be carriers, and therefore the couple would not be detected as an at-risk couple.

Second, when you do such testing there is a small, 1 in 200, but significant probability that a child carrying the sickle cell gene is the result of nonpaternity. Thus a delicate and potentially explosive situation may be created.

Up to this point I have emphasized counseling for couples at risk of having a child with sickle cell disease. I have not forgotten the counseling of patients like J.W. who have

sickle cell disease. In essence, the principles of nondirective counseling should be applied to persons affected with sickle cell disease as they are applied to carriers of the sickle cell gene.

Special consideration must be made in working out their psycho-social problems, and perhaps in being certain that these persons understand the increased recurrence risk for sickle cell disease if they should mate with a person who carries one of the hemoglobinopathy genes, and the absolute certainty of having an affected child if they should mate with a person who also has sickle cell anemia.

The problems of increased maternal and fetal risks in the pregnancy of patients with sickle cell disease will be of serious concern, regardless of the possible genetic makeup of the offspring. But the decision of what reproductive options to chose must rest with the couple after they have been fully informed of all consequences. This is in spite of our serious concerns about the high costs of medical care for patients with sickle cell disease in a climate of rising overall medical costs.

With the availability of methods of identifying couples at risk in well-run screening and counseling programs, and the introduction of ways to diagnose hemoglobinopathies prenatally, we are increasingly faced with the dilemma of whether to focus our efforts on prenatal diagnosis or to emphasize treatment for this quite variable clinical disorder. We are then faced with a decision about the relative value and quality of human existence. In the most humanitarian spirit of medicine, we should focus on prenatal diagnosis primarily as an interim measure, or as a technique by which we might eventually introduce prenatal treatment for sickle cell disease.

In the meantime, the efforts already begun to make all modern medical professionals conversant with those genetic principles that will allow persons at risk to plan their reproductive future should be continued.

THE HEMATOLOGIST'S PERSPECTIVE

Helen Ranney, M.D.

This panel includes Dr. Howard Pearson and Dr. Darleen Powars, both of whom have had extensive experience in pediatric hematology. I will not take much time since these two speakers have had more experience than I in working with this disease. I would like to comment, though, on a few of the problems posed by this case and indicate some of the questions to be addressed concerning the management of sickle cell disease.

For example, is there anything that should have been done differently in handling J.W.? The child had a rather low hemoglobin, around 6 grams percent through recurrent admissions. Should he have been transfused during childhood since he had recurring episodes of the hand-foot syndrome, as well as other manifestations of sickle cell disease?

A second question refers to genetic counseling and deciding which patients should be offered the option of antenatal diagnosis. Is it justifiable to subject the mother and fetus to the possible complications of experimental procedures involved in obtaining fetal blood if no subsequent action will follow? I doubt that one can justify the risk of the prenatal testing simply on the basis of providing information to the family when that information could later be made available by testing cord blood.

The question of who should be eligible for antenatal diagnosis of sickle cell disease has not been discussed much because antenatal diagnosis is still experimental and rather infrequently performed.

We all agree that a few patients with sickle cell anemia, in any series, account for most of the hospital admissions. A few patients with sickle cell anemia have much more illness, many more crises or other complications of sickling than do others. Indeed, Dr. Serjeant has emphasized the large number of relatively healthy patients with sickle cell anemia in Jamaica, and we certainly have seen this kind of patient in this country.

Perhaps antenatal diagnosis could be more useful to a family seeking counseling that already has a severely affected child, although I do not think it could ever be strongly recommended considering the risks to the mother. If one child is severely affected, is it not more likely that another child with sickle cell anemia might be severely affected? Antenatal diagnosis for a couple that has no children with sickle cell disease, or only a mildly affected child, may be more difficult to justify. Perhaps in the future we will be able to modify the manifestations of sickle cell anemia by treatment, and mild sickle cell diseases would be less of a problem for patients. In a good many genetically-determined disorders, the management of symptoms receives more attention than genetic counseling.

A better treatment for sickle cell anemia derived from research may be a more realistic hope for therapy of sickling than the extensive use of antenatal diagnosis, even if antenatal diagnosis were safe, readily available, and better than 99 percent reliable.

THE PEDIATRICIAN'S PERSPECTIVE

Darleen Powars, M.D.

J.W.'s case is representative of many of the problems that we commonly see in the growing youngster with sickle cell anemia. When evaluating this patient throughout the 16 years of his life, as observed by Dr. Pearson, it is clear that this child began to show the pattern of his individual illness early in his life. He demonstrates the natural history tendency to have similar, repeated clinical episodes.

If the child survives the devastating first two or three years of life, when the risk of rapid death from septicemia or splenic sequestration crisis is paramount, and lives into the fourth year of life, the child begins to develop the consistent pattern of his illness. This pattern is frequently set by seven years of life and from this a valid prediction can be made regarding future expectations. One can predict for this child a lifetime of bone problems.

Interestingly enough, family members may not follow the same consistent pattern of illness. A family may have one child with a large number of infections with frequent episodes of pneumonia, and another youngster, similar to the young lad here, showing the lifelong problem of his organ-specific bone disease. Bone problems in sickle cell anemia are among the major problems causing considerable pain and disability over a long period of the patient's life.

We are currently in the process of an in-depth evaluation of our population with sickle cell disease. Figure 20 shows the demographic cohort of patients in Los Angeles, now consisting of 464 patients, who have been followed for a specific period. There are 357 patients with sickle cell anemia, equal numbers of males and females, and a large number of admissions. It is clear in our population in Los Angeles during the last 15 years that it is indeed the SS group who is at great risk.

Figure 21 provides background information regarding the age of our patients. This figure shows the problem that plagues the pediatrician, that is, death during the first decade of life and usually within the first five years of life. We observe a high incidence of death in children, modal age of death of the youngster at 25 months of age, and many of those children have infectious diseases.

	TOTAL	MEN	WOMEN	ADMISSIONS	DEATHS	
PATIENTS STUDIED	464	223	241	2613	53	M 25
						F 28
SS	357	172	185	2262	44	M 19
						F 25
SC	89	42	47	291	9	M 6
						F 3
S THAL	10 (S-β°6, S-β⁺4)	4	6	44	0	
S-OTHERS	8	5	3	16	0	

Figure 20. Demographic cohort of patients with sickle cell disease in the Los Angeles County -- University of Southern California Sickle Cell Center, September 1975. Seventy-five percent of all patients are SS.

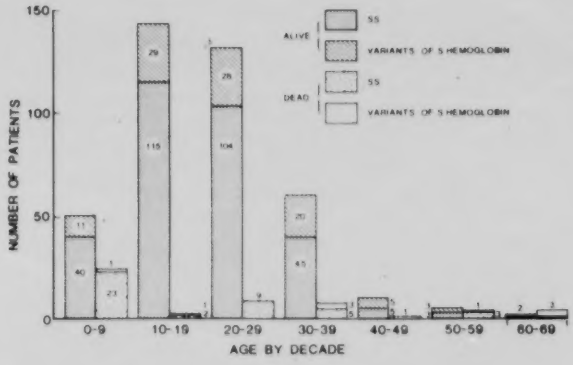


Figure 21. The risk of death is greatest during the first decade of life. Eighty-seven percent of all patients are currently alive.

Note that there are many patients living well beyond the first decade of life. There are patients in Los Angeles found living to be 50 and 60 and up to 69 years of age.

As demonstrated by the latest run of the computer-assisted study of the Los Angeles demographic group of patients, one observes a distinct difference in the morbidity of the fourth decade male patient, as compared with the fourth decade female patient. The young man

who has grown into maturity, age 30 to 40, can be shown to have more morbidity and more major problems than an equal cohort of women in that same age range. Much of the morbidity is related to bone disease. Understanding the growth and development of children who are in the active growth phase is essential in this context.

J.W. has grown into the second decade of life and we expect that his third decade of life will be marked by progressive degenerative bone disease.

There is a changing pattern of the bone disease as the patient matures. During infancy, an important characteristic of the bone marrow must be considered. In young infants, the bone marrow is diffusely distributed throughout the bones, including the phalanges and small bones of the hand. However, as the child grows, the marrow tends to centralize into the bones of the central cavities of the body and femur. We observe a close correlation between the infarctive patterns and avascular necrosis that one observes clinically, depending on the localization of the bone marrow cavity. There appears to be a "competition" between the hematopoietic stem cells making blood and the osteoblasts making bone. As the bone cortex becomes thicker during the second decade of life, this is associated with further centralization of the marrow areas.

The nutrient artery of the bone provides the blood supply to the diaphyseal portion of the bone in both children and adults. In infants and growing children, the growth plate actually prevents the perforation of the methphyseal vessels into the diaphysis. As a consequence, the infant is more dependent on a single system of nutrient vessels to his bones than is an adult. Also, in infants the periosteum is loosely attached to the bone with poorly developed periosteal vessels. This partially explains the propensity for avascular necrosis to occur along the shaft of the bones as so commonly seen in infants and children but rarely in adults. The major manifestations of bone sickling include three types of avascular necrosis specifically related to age and location of the lesion: 1) the hand-foot syndrome, 2) diaphyseal shaft infarcts, and 3) aseptic necrosis of the femoral and humeral heads and vertebral bodies.

Considering the vascular supply to growing bones as a result, what do we see? Following a precipitating illness, often viral in etiology, we begin to see the swelling of the hands and feet with the involvement of those small bones of the hands and feet, the hand-foot syndrome.

There is almost no other condition, except for two cases of mercury poisoning during infancy that I have personally seen, in which patients have generalized nontraumatic painful hands and feet. This syndrome is really pathognomonic in little children with sickle cell anemia. It is self-limited. It is excruciatingly painful. It spontaneously abates after two to six weeks. The hand-foot syndrome has a tendency to recur time and time again.

After the third or fourth year of life, as the bone marrow contracts, the patient has less sickle crisis manifestations involving the small phalanges or the metacarpals or metatarsals and begins to have more diaphyseal bone problems. He has the rather classic bone infarct of the central shaft of the main bones. The mid-childhood infarcts usually include the tibia, humerus, and femur. Cortical bone infarcts along the shaft tend to be more localized to a limited area, particularly in patients over five years of age. These infarcts manifest themselves by areas of spot tenderness, erythema, pain and swelling, totally clinically indistinguishable from areas of acute bacterial osteomyelitis.

Bohrer in Nigeria observed more bone infarcts in males than in females, but 50 percent of his patients were less than five years of age. On the contrary, in the United States we find bone diaphyseal infarcts frequently occurring during late childhood and adolescence.

Aseptic necrosis of the femoral and humeral heads, along with the vertebral bodies, is the next predictable manifestation of bone disease expected in this youngster. The x-ray appearance differs depending on the state of closure of the epiphyseal plate. Prepuberal x-ray findings are identical to those seen in Legg-Perthe's disease. After puberty there is more segmental destruction. The hip lesions cause more difficulty to the patient because of the constant stress of weight bearing.

Although it is frequently stated in the medical literature that SC patients have more femoral head disease than SS patients, in a review by J.P. Harvey and Townsend at our institution, more major disease was found in our SS people.

Figure 22. Radiograph reveals the first tibial diaphyseal infarct in this SS patient at age 2.

Figure 23. At age 6, the tibia shows the radiologic effects of repeated bone infarcts; the "bone-in-bone" appearance.

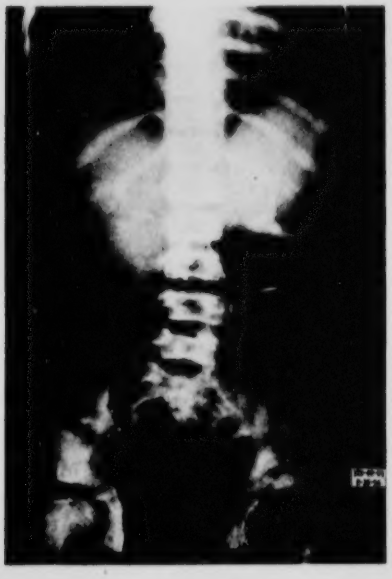


Figure 24. By age 8, the femoral head and vertebral bodies are involved.

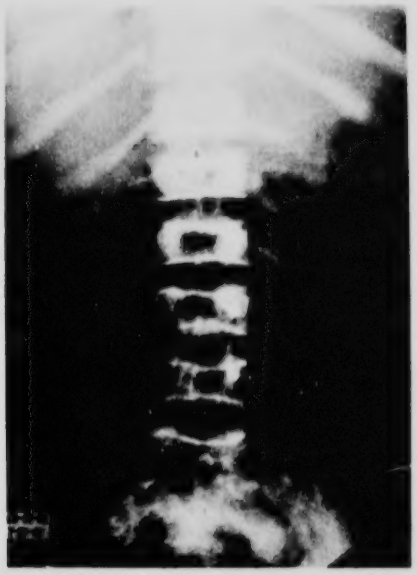


Figure 25. Severe involvement of the lumbar dorsal spine is clearly evident by a "fish mouth" deformity by age 16.

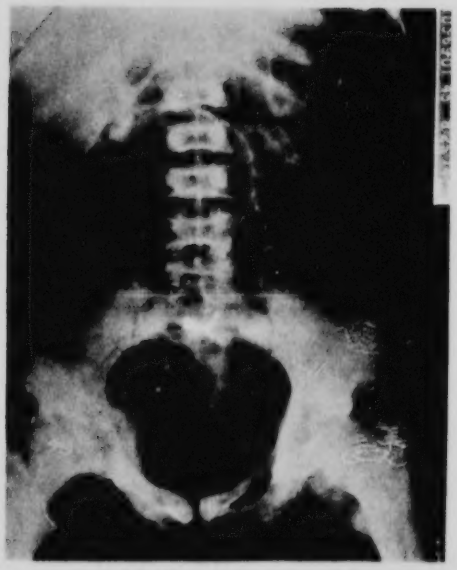


Figure 26. At 27 years of age, there is marked flattening and distortion of the femoral heads with severe pain on weight bearing.

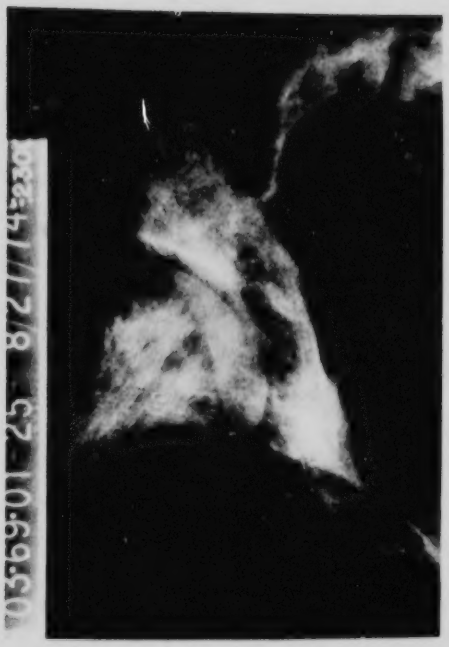


Figure 27. The vertebral bodies in the lower spine are severely damaged and associated with chronic back pain.

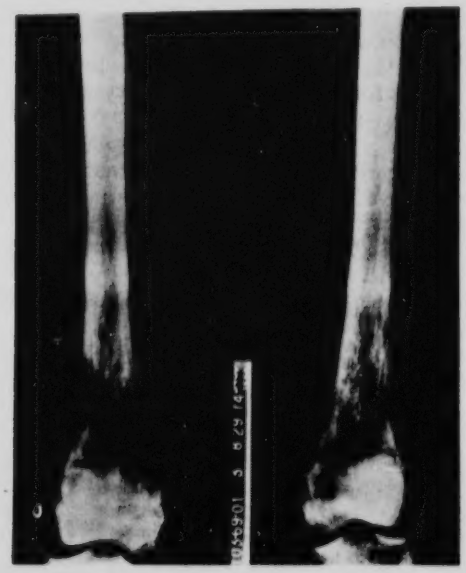


Figure 28. The distal femur shows the radiologic findings of patchy rarification at age 27.

This simply reflects the current better survival of SS patients to an older age into the third and fourth decade.

Figures 22 through 28 are representative radiographs taken of the same young man over a 25-year period to demonstrate in a single patient the changing pattern of bone involvement. In the young person growing up with sickle cell anemia, one can see progressive increase in the diaphysis or long bone changes becoming more pronounced after each sickle crisis.

In a young child, wide open space of the medullary canal in the femur is observed with intact and excellent femoral heads. By the time the patient reaches puberty or age 17, the long bones demonstrate cortical thickening and show the heavy dense cortical appearance that the internists see in the adult patient. This is often called the "bone in bone" sign.

Within a 10-year period, in a representative case, the femoral head has begun to show flattening. This young man has progressed to bilateral severe hip disease along with two vertebral bodies and one humeral head becoming involved in the same process over the next ten years.

The natural history of the bone disease progresses centrally and follows the pattern similar to that of the bone marrow. Early in life, bone involvement is distal. It begins to move into the central portion of the long bones with major diaphyseal involvement and, as an end-stage in the adult, affects those great bones that must support the body, the femoral and the humeral heads, and vertebral bodies. It is rare for an adult patient to have a hand-foot syndrome or to even really have diaphyseal bone infarcts. We have long since learned that if a patient over 16 comes in with what appears to be a bone infarct, the chances are very good that his sickle cell osteitis is due to a Salmonella infection, whereas in the 7-year-old child with identical physical findings, cultures will often show no specific organism, and we have indeed an aseptic osteitis. The radiographic and clinical findings of avascular necrosis and septic osteomyelitis are indistinguishable.

Figure 29 shows the hospital admissions of all patients by age. In observing a population of patients as they grow older, we are beginning to see a very distinct pattern of illness in the adult population. The female patients have a peak in their morbidity that begins at age 15 and continues through age 35. This is due to procreative-related activity, such as complications of birth control methods, pregnancies, and abortions.

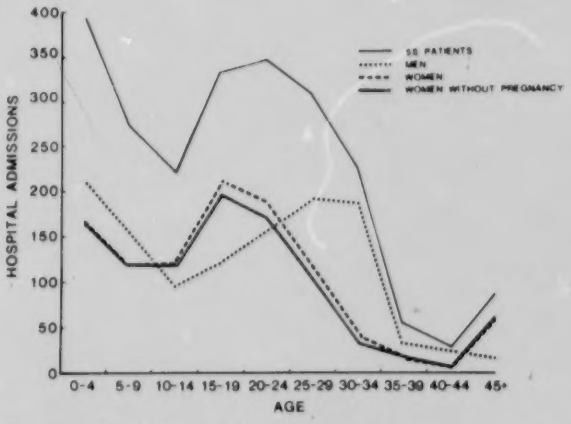


Figure 29. Morbidity patterns based on the Los Angeles Natural History Study show an increased number of problems in the male patient during the fourth decade of life.

The male patients, beginning in the early 20s, show an unexpected rise in their morbidity. This third and fourth decade male population accounts for the major morbidity of the group. Half of the morbidity in the fourth decade of life of male patients is related to severe devastating bony complications, making it extremely difficult for them to do hard labor or any type of work that requires physical strength. The weight-bearing problems of the femoral head disease are very real, but the problems of the humeral heads not allowing adduction motions make it very difficult for a man in his more mature years to find employment.

The young man discussed here will have persistent bone problems during the next 15 or 20 years. He will have fewer of the so-called life-threatening problems that he had as a little child, but he will begin to have the chronic and devastating bone disease that will affect his life style and will become his major problem. It would be ideal if we could find a safe agent that could be used to prevent the patient from sickling all these many years, and preclude some of these chronic problems.

THE CARDIOLOGIST'S PERSPECTIVE

William F. Friedman, M.D.

It is appropriate for a cardiologist to participate in this symposium since the sickle cell disease was first described in 1910 by a cardiologist, James Herrick, and in that very first patient there was evidence of a large heart associated with significant cardiac murmurs. There are a number of specific cardiovascular stresses that exist in the patient with sickle cell anemia that should be discussed before focusing on the diagnostic dilemma of distinguishing sickle cell disease from rheumatic fever.

These stresses include an elevated cardiac output, which in large part is the result of a reduction in the oxygen-carrying capacity of the blood. In addition, there is some arterial oxygen unsaturation largely due to pulmonary problems, including the decreased oxygen affinity of the hemoglobin itself with a marked shift to the right. This makes oxygen pick-up at the alveolar level more difficult, although it does indeed facilitate delivery at the tissue level.

Another stress is created by the ventilation-perfusion abnormalities within the lung, and pulmonary right-to-left shunting. Moreover, especially in the fourth decade, there may be thrombotic pulmonary vascular disease that may actually progress to such an extent that pulmonary hypertension and right heart failure ensue.

Lastly, there has been a great deal of speculation about the existence of specific myocardial dysfunction, that is to say, a problem with cardiac contractility. Speculation exists that myocardial dysfunction may be due to microvascular myocardial disease. In this regard it is of interest, as Dr. Ranney alluded to in her earlier remarks, that the incidence of major occlusive coronary disease in patients with sickle hemoglobin is unusual. Baroldi, in an examination of about 53 autopsied hearts of patients with sickle cell disease, found no evidence of myocardial ischemia.

In contrast, a study from New Orleans found microvascular disease in the end coronary arteries. If one looks at a gross and microscopic picture of the heart at autopsy in patients with sickle cell disease, one sees just myocardial wall thickening, some individual fiber hypertrophy, and only nonspecific, patchy areas of degeneration.

The major hemodynamic problem in SS patients appears to be the increase in cardiac output, and that is due less to altered blood viscosity than it is to peripheral vasodilation. Thus, the heart can unload to a lowered systemic vascular resistance. There are limited ways in which the heart can increase its output, including keeping the same stroke output and increasing heart rate, or by increasing the extent of shortening of the myocardium at the same heart rate and thereby increasing stroke volume. The patient with sickle cell disease uses this latter mechanism in particular. Hence, part of the cardiomegaly seen in patients with sickle cell disease is really compensatory and expected, and helpful to the patient.

As in patient J.W., it is not at all unusual for problems to exist in diagnostically distinguishing acute rheumatic fever from sickle cell disease because there are many shared signs and symptoms between acute rheumatic fever and the crisis of sickle cell disease.

Sickle cell disease symptoms include fever and joint pain, as J.W. had, along with nosebleeds, abdominal pain, and shortness of breath. A large heart and an overactive precordium are seen in both sickle cell disease and rheumatic fever. The prolongation of the P-R interval on J.W.'s EKG is a nonspecific finding. It may be due to an altered autonomic tone in the patient with sickle cell disease, and it certainly is not diagnostic of rheumatic fever.

Heart murmurs are generally present in every child or adult with sickle cell disease, and these heart murmurs may be quite varied. Commonly, one hears ejection murmurs over the base of the heart as the result of increased flow across either the aortic valve or the pulmonic valve. In the child with sickle cell disease who has a 50 to 100 percent increase in the cardiac output at rest, the presence of a murmur may not mean there is intrinsic valve disease.

In addition, diastolic cardiac murmurs may be audible, and these also do not necessarily imply that a problem exists with the anatomy of the atrioventricular valves. Increased flow across both the mitral and the tricuspid valves may also produce these diastolic murmurs.

One of the problems in making the distinction between rheumatic fever and sickle cell anemia is that there is no specific diagnostic test for rheumatic fever. Diagnosis is arrived at by a compilation of major and minor findings following the Duckett-Jones criteria. The presence of two major criteria or one major criterion and two minor criteria indicate a high probability of acute rheumatic fever, especially if there is evidence of preceding streptococcal infection. One must search diligently, either by throat culture, by ASLO titer, or by other tests for indications that a streptococcal infection has been present.

The major manifestations of rheumatic fever include carditis, polyarthritis, chorea, erythema marginatum, and the presence of subcutaneous nodules. The minor manifestations include fever, joint pains, and a past history of rheumatic fever or rheumatic heart disease. Laboratory findings that include the acute phase reactants, the erythrocyte sedimentation rate, the C-reactive protein, an elevated white count, and the P-R interval are also minor manifestations.

There are a few clues that may be helpful in distinguishing sickle hemoglobinopathy from acute rheumatic fever, but none of them really were present in J.W. When one hears the murmur of aortic regurgitation, it almost always means that an organic valve lesion exists and one may assume that acute rheumatic fever and carditis are present. Also, the size of the left atrium, diagnosed either by EKG or by echocardiography may be helpful in distinguishing between the two diseases. In mitral regurgitation lesion, the left atrium may be expected to be much larger than in simple high-flow situations, such as exist in sickle cell anemia.

In addition, one can detect the presence of a pericardial effusion, usually by echocardiography. The presence of effusion usually signifies that rheumatic pancarditis is present. Moreover, abnormal mitral motion by ultrasound examination may be of significance, especially if you think the patient had previous rheumatic disease. Mitral stenosis is not a sequela of sickle cell anemia. Lastly, one may receive help diagnostically by viewing the response to salicylates which can be extremely dramatic and very efficacious in the patient with acute rheumatic fever.

As far as J.W. is concerned, there really was no evidence of preceding streptococcal infection. The patient really got well very rapidly. If you took a close look at his chest x-ray, there was really only mild cardiomegaly. The fact that the murmurs defervesced after the drop in the patient's temperature is a response to acetaminophen and not a response to salicylates. I do not think that a major concern existed about acute rheumatic fever in this patient. Attention was directed properly at the patient as suffering from sickle cell crisis.

THE NURSE'S PERSPECTIVE

Sylvia L. Lee, P.H.N.

The role of the nurse in the Comprehensive Sickle Cell Center is quite broad. Figure 30 shows some of the things in which the nurse may be involved. She provides for continuity of patient care, assists in patient and family education, coordinates patient activities and referrals, gives physical and emotional support, and serves as the patient's advocate both in care and research. The nurse's role, whether in sickle cell disease or any illness, is "caring" for the patient.

Figure 30. Role of the Nurse:

- Provides for the continuity of patient care
- Provides for patient and family education
- Coordinates patient activities and referrals
- Gives physical and emotional support
- Serves as patient advocate (care and research)

I would like to share with you some of the methods and indications for caring that may be related to the case presented. The single most important factor in caring for the patient in sickle cell crisis is a positive attitude toward the disease and the prognosis. The role of the nurse is to foster this positive approach.

After the diagnosis is made that a child or an adult has sickle cell disease, the nurse arranges a family conference. The conference is a good starting point for developing a relationship between the family and health care team. The family should receive support from the team and also some insight into the nature of the illness. Immediately after the conference it is important to make sure that the family knows what to do, especially when problems occur, how and where the nurse may be reached, and how to obtain medical assistance in case of an emergency, particularly at odd hours.

Teaching the patient and his family about sickle cell disease should be initiated as soon as possible after diagnosis to reduce the anxiety produced from fear of the unknown. Everything cannot be taught at once. Therefore, teaching should begin with some of the steps listed on Figure 31.

Figure 31. Family-Oriented Educational Emphasis:

- Evaluation of known information
- Clarification of misconceptions
- Explanation of Sickle Cell Disease
- Care of patient
  - when in crisis
  - when not in crisis
- Special problems (when appropriate) FUO, enuresis, priapism, gallstones, strokes, etc.
- Planning for parent and/or patient groups

First, we should recognize the importance of evaluating the information the family already has to determine educational goals. After we have clarified some of the misconceptions, we can discuss how sickle cell disease may affect that family and give some indications for medical management. We should also discuss how to care for the child when he is not in crisis. There are certain special problems that should be discussed when appropriate or when problems occur. Such problems may include fever of unknown origin, enuresis, priapism, gallstones, and strokes.

It is important to introduce the idea of parent and patient groups. This is the way some families will obtain most of their education. They will have an opportunity to share with other people in the group and feel they are not alone in some of the decisions and problems confronting them.

When conducting parent and patient groups, we should use caution in giving information so as not to frighten people. Sometimes those who give information have a tendency to try to discuss everything about the disease all at once. This is not necessary. Many times this is so

frightening that people will anticipate things happening when they really are not going to happen at that time at all.

Whenever problems are likely to occur, it is good to have a plan of action ready. In case of sickle cell crisis, if the patient and his family know what to do when a problem occurs, the anxiety is reduced. A representation of such a plan is given in Figure 32.

Figure 32. General Management in Pain Crisis:

- Take temperature
- Obtain medical advice
- Force fluids
- Apply moist heat
- Encourage "progressive" ambulation (excessive bedrest should be avoided)
- Encourage food intake
- Provide physical comfort
- Give emotional support

When the temperature is elevated, medical advice should be obtained. Fluids should be encouraged and moist heat should be applied to the affected area. Bed rest is not always necessary. Progressive ambulation is encouraged. Food intake is important along with physical comfort and emotional support.

Many times parents want to know if there is anything that can be done to prevent a crisis. Although there is no cure or specific treatment or preventive medication for sickle cell disease crises, we need not feel defeated. However, if we explain factors and conditions that are likely to precipitate a crisis, we may be helpful in preventing some aspects of the problems. Figure 33 lists some conditions that may precipitate or contribute to a sickle cell crisis.

Figure 33. Conditions Thought to Precipitate or Contribute to Sickle Cell Crisis:

- Dehydration
- Infections
- Extreme fatigue
- Severe emotional stress
- Over-exposure to cold or heat

Dehydration is probably the first factor that should be considered. An elevated temperature may indicate infection, which is sometimes believed to precipitate a crisis. An increase in the patient's stress and strain may precipitate a problem. Over a period of time, we may find that children are sometimes unnecessarily exposed to heat or cold, causing them some problems.

When a patient is feeling well, it is often necessary to remind him that he has sickle cell disease. Very often it is necessary to remind him to visit the doctor. When the patient is well, he seems to deny the fact that he has sickle cell disease. We need to provide well-child care, not only to remind patients of their illness, but also to be prepared when illness occurs. We emphasize to families the importance of regularly scheduled doctor's visits or appointments to the clinic. We need to know how a patient is doing when he is well so as to provide baselines during illness.

Figure 34 details the steps in a well-child care program. We encourage a complete program of immunization. Visits to the dentist are essential because even dental infections may precipitate a crisis. Eye examinations are important too, especially to those with hemoglobin SC disease.

Figure 34. Well-Child Care:

- Regularly scheduled visits to doctor or clinic
- Immunizations
- Dental care
- Eye examinations
- Participation in extra-curricular activities

Participation in extra-curricular activities is very important to children. The child with sickle cell disease will feel he is as normal as other children if he participates. He will not concentrate on his own problems exclusively, but will be right in the mainstream of activity.

When patients and their families have had good emotional support from the time of diagnosis and through some of their problems, they are usually reasonably comfortable in treating

a crisis at home. The exception might be the family of a newly diagnosed patient experiencing the first crisis. With the first illness, families often have many anxieties and may need support in managing the patient.

Very often parents recognize when the child's behavior is different. They can call the physician and do the necessary things to support the child, realizing he may be in an early stage of crisis. Parents will usually take the child's temperature; if there is fever they will call the nurse or the hospital. When the nurse is reached, she discusses with them what can be done or what should be done when the child is not feeling well. This may be referred to as telephone management, as described in Figure 35.

Figure 35. Telephone Management of Sickle Cell Crisis:

- What is the problem?
- Does the patient have a fever? How high?
- Does the patient have pain?
- Is the patient's pain his usual type or crisis pain?
  Where is it, how severe, constant or intermittent?
- How long has it been going on?
- What is patient doing for the pain?
- Are there any other complaints?
- Does patient feel he is in crisis?

In telephone management of sickle cell crisis, the nature of the problem and its relationship to sickle cell disease should be determined first. The next concern should be fever. Does the patient have a fever? How high is the fever? Following these questions there should be questions concerning pain. Does the patient have pain? What kind of pain and where is the pain located? Is it the kind of pain the child usually has when he is in crisis? Sometimes children have stomachaches which may or may not be related to sickle cell disease.

The nurse may also ask questions such as: How long has the pain been going on? Is it severe? It is constant or is it intermittent? What are the parents doing for the pain? What is the child doing for his own pain? Has he taken any kind of medication? Does he usually take medication? Has he applied moist heat and increased his fluid intake? Are there any other complaints?

Sometimes, while talking with the parents, it can be decided if the patient is actually having a sickle cell crisis. Every patient's complaint is not a crisis. However, there could be other problems, such as a developing infection that needs treatment. Does the child feel he is in crisis? Do the parents feel their child is having a sickle cell crisis? These are some of the things that can be investigated while on the telephone so that management of the crisis can begin.

It should be made clear to the parents and to the patient that when the patient is at home and trying to manage a crisis, if he feels uncomfortable at all, someone should call the nurse or hospital or the patient should come in to be evaluated by the physician.

To be more comfortable in diagnosing and treating crisis by telephone, the nurse should know the family very well, know how it responds to anxiety and how the family responds to sickle cell disease itself. We should be aware and sensitive to all of the family's needs, the things it is saying and the things that it would rather not say. We should keep in touch with the family until the crisis is over. The nurse is also responsible for follow-up patient care and for making patient appointments when necessary.

THE SOCIAL WORKER'S PERSPECTIVE

Delores Duncan, M.S.W.

I would like to take a look at J.W.'s case from two different standpoints: first, from the standpoint of what could have been done in terms of prevention, or in terms of helping to overcome the development of secondary and tertiary psychological and social disabilities; and then second, to look at what can be done once the psychosocial disabilities have developed.

As in any illness, early intervention is essential. Early social work intervention is essential in the identification and assessment of existing difficulties and familial situations which contribute to the development of psychosocial disabilities in SS patients.

In the evaluation process, economics, parental knowledge regarding sickle cell anemia, the clearing up of misconceptions, and the replacement of ignorance and fear with reassuring supportive services become major areas of focus for the social worker. The social worker must bear in mind too, that parental understanding of the illness, parental feelings and attitudes, their own coping abilities and experiences in life, all influence the sickler's perception of himself, the quality of adjustment that he will make, and the preparations that he will make for life.

Subsequent to the evaluation, close follow-up is necessary to maintain open channels of communication and to foster ongoing understanding and provide supportive services whenever the need arises. For this reason, it is absolutely necessary to have a close, open relationship among the major institutions providing services for the sickler and his family. In this particular case I would like to identify the three major institutions as the home, the school, and the health-care provider.

The social worker often becomes the coordinator and the liaison person among these institutions, and as long as difficulties can be identified at an early stage, they do not have to be devastating for most of our sicklers.

I would like to now turn to some of the physical characteristics that have been identified in J.W.'s case and mention some of the psychosocial implications and what can be done to overcome these implications. The problem of enuresis can be upsetting and embarrassing, not just for parents, but also for the child. The child should not be made to feel guilty about the enuresis, and care should be taken that he does not smell of urine in school. Ignorance of the child's needs can only lead to feelings of rejection, a damaged self-concept, and further withdrawal. Both parents and child should be reassured that the enuresis does not persist for life.

Another problem is the episodic hospitalizations. Recuperative periods in the hospital and at home result in poor school attendance and interruptions in the socialization process. But these recuperative periods do not have to produce frustration, poor academic performance, a sense of failure, and withdrawal. Fortunately, referrals to the home-bound teacher or the visiting instruction corps can be encouraged and the child's academic program should resume once his physical condition improves. Referrals to volunteer tutorial programs, developed or approved by the sickle cell staff, can also help to overcome academic weaknesses and build on areas of strength.

Socialization can be encouraged, both at home and in the hospital during recuperation. Most hospitals are equipped with a play or child life program which provides supervised recreational activities for those who are physically able to participate, including wheelchair-bound patients. Encouraging socialization will help the patient to overcome problems of withdrawal and make frequent hospitalization more bearable for both younger patients and adolescents.

Prevocational counseling should stress the fact that sicklers do live beyond the teenage years and are capable of seeking and maintaining employment, and therefore, must make plans for their lives. Emphasizing these facts will help to ensure the SS patient's successful completion of high school, vocational training, or a college program, and job placement. These kinds of programs also help to foster self-confidence

and help to offset academic deficiencies and failure which lead to dropping out of school.

The problems of poor academic performance and dropping out of school can be compounded by lack of understanding of sickle cell anemia on the part of the patient and his family. The patient's difficulties may also be compounded by emotional problems associated with characteristics of the disease, such as lack of stamina, small stature, and delayed maturation. To compensate, the patient should be encouraged to pursue and excel in such activities as crafts, the arts, music, and drama, and to participate in youth groups, boys' or girls' clubs, sororities or fraternity groups. These kinds of involvement do not have to take the form of physically strenuous activities and can be ego-building, challenging, and rewarding. They also can help the patient to gain respect among his peers.

Parents, teachers, and hospital staffs have to be mindful of treating the patient according to his chronological age. For example, if a child who is 16, as in the case of J.W., looks 11 years old, one should refrain from humiliating gestures such as lifting that child and placing him on the examining table. This can be devastating for the male adolescent ego. Any negative gesture or remark regarding small stature and delayed maturation can only serve to compound the adjustment. Parents, especially, need to accept the patient's size, rather than constantly expressing their wish to have a tall son or to have him gain weight. Parents must also refrain from constantly comparing the child with siblings and other relatives.

It is becoming the natural way of dress these days for men to wear higher-heeled shoes to boost their smaller stature, whether or not they have sickle cell anemia. And this is something that the male sickle cell patient can do. Women have always had this advantage, in addition to all the make-up and prostheses that contribute to a more mature look. Hence, females have an easier time adjusting to SS characteristics.

In the breakdown or absence of these preventive measures, a program of rehabilitation -- social, educational, vocational, and psychological -- must be instituted. Therapy involving some of the previously suggested therapeutic measures should be offered to help the SS patient overcome emotional problems. Ascertaining some base knowledge of the patient's educational capabilities and interests, in addition to offering vocational assessment and guidance, is absolutely necessary.

The patient's education regarding his illness should be assessed, and enough information given to aid in his adjustment process. Even though the task of rehabilitation is more difficult than prevention, each step toward overcoming a disability is a source of motivation for successful rehabilitation for patients such as J.W. All of the difficulties exemplified in this case are frequently encountered by either the psychologist or the social worker in the Comprehensive Sickle Cell Center.

As I said before, early intervention, social evaluation, knowledge of resources, appropriate referrals, parent and patient education, ongoing counseling and follow-up on the part of a resourceful social worker, can help to restore and maintain stability in this kind of patient. However, success in prevention and rehabilitation depends to a large extent on the sensitivity of the medical team to the total needs of the patient, and on the emphasis that the medical team places on total patient care.

Because of the large group of young SS patients within our sickle cell center, we have formed a patient group to cater to the needs of this particular age group -- 16 through 30. We find that peer support can be of great benefit to these patients, along with the supportive therapy that the staff provides.

DR. PEARSON: Dr. Murray mentioned, and Dr. Ranney further commented on, prenatal or antenatal sickle cell diagnosis as a viable means of sickle cell counseling. Perhaps Dr. Murray could tell us how feasible this procedure is. Is this something patients in St. Louis and other parts of the heartland of America can take advantage of, or is it investigational and available only in a few centers?

DR. MURRAY: The availability of this technique is quite limited. I am concerned with the expansion of fetal blood sampling technique in the wake of the Secretary's statement that amniocentesis has been accepted. In the minds of the general public prenatal diagnosis is equated with amniocentesis. They tend to think of the two procedures in the same sense.

In considering the availability of this technique, there is also the problem of the family that already has had one or more affected children and is anxious not to have additional affected children, particularly if their children have been severely affected.

I can also foresee such families spending large amounts of money to get to those few centers where the technique is available, to try to determine the diagnosis of the potential offspring. This urgency may lead to extension of this technique. This may be unwarranted and unnecessary since one member of our own staff, and investigators elsewhere, are working on methods of making prenatal diagnosis of hemoglobinopathies in single red blood cells. This would enable us to use the few red blood cells found in the amniotic fluid as a testing source.

If this technique were possible, it would not be necessary to tap placental blood vessels. Prenatal diagnosis of hemoglobinopathies would be technically as easy as amniocentesis if these laboratory methodologies are developed.

Although at the moment this technique is not generally available, with pressure from families who are upset that they have several affected children, with pressure by state and government agencies who are interested in saving money and being cost-effective in their approach to this problem, or with the development of newer techniques that allow the diagnosis to be made without invasion of the placenta or the fetal circulatory system, this technique could spread very widely and rapidly.

We should try to make a decision early whether or not we are going to pursue this technique as a significant option in handling the problem of sickle cell anemia.

DR. PEARSON: Are there specific comments by the panel or members of the audience?

DR. MURRAY: I would like to make one other comment concerning an earlier remark about mothers having to terminate pregnancy once they have gone through the process of prenatal diagnosis. I feel there are strong ethical and moral reasons why parents who decide they want the information obtained through this rather risky experimental procedure should not be forced to have an abortion as a consequence of having taken advantage of prenatal diagnosis. They may, for a variety of reasons, decide to take their chances with the child's illness, or its severity. The parents may have personal, religious, or ethical reasons for not terminating a pregnancy. They may simply want to know as early as possible whether their child is affected so they can make appropriate preparations. I think this option should not be closed to them if they wish to take advantage of this technique.

DR. RANNEY: I would like to respond to that because I obviously initiated that part of the discussion.

No one favors "forcing" abortion on any pregnant mother. The question is whether the risk to mother and fetus of an experimental procedure is justified if no decision is to be based upon the results of that procedure. We have had little experience with antenatal diagnosis since there are relatively few centers at which it can be done. Any new procedure carries some risk, not only for the mother but for the fetus. A family that requests antenatal diagnosis should understand the risks. If they are unwilling to consider terminating pregnancy, there would be much less risk in establishing the diagnosis by studies of cord blood at the time of delivery.

There is no justification for "forcing" abortion on the basis of the results of such tests. But there is an obligation to explain clearly to the patient the risks of the procedure to be carried out.

DR. MURRAY: It is a function of people having different value systems and different ways of looking at the quality of life, and also some people's desire to know if their child will be healthy, even though the outcome may be unpleasant.

In the case of sickle cell disease, you would not necessarily require termination of pregnancy as a condition of prenatal diagnosis. But by excluding the option of antenatal diagnosis, you would be preventing people from being able to take advantage of information they feel important for them to have.

This has been debated very hotly in genetic circles primarily because of the limited resources for performing prenatal diagnosis. Should people who decide against an abortion, regardless of the test outcome, be precluded from prenatal diagnosis in the first place?

There are many reasons, even though others may fail to understand them, why people may seek this information, fully aware of the risk to the fetus, and fully understanding the clinical course that follows once an affected child is born -- and yet refuse the option of terminating the pregnancy. I think it is really a question of impressing our value system on someone else. I do not think this is something we should choose to do.

DR. FRIEDMAN: On the one hand you seem to be talking about a relatively noninvasive amniocentesis that is used for all other genetic diagnoses, while on the other hand you are talking about a more extensive invasive procedure that is not currently available. Don't you think the issue of relative risks does play a role? I have difficulty understanding what compelling information would be sought that the parents could not wait for a few more months if they were not going to do anything with that knowledge anyhow.

DR. MURRAY: The ethical principle I am discussing concerning people's right to have the information and knowledge has nothing to do with the risk involved. We are talking about the principle of people's freedom to choose to take certain courses of action. The principle does not have anything to do with the medical risk, the knowledge to be gained, and so on. And I think this is where physicians, who tend to think scientifically, become confused with moral and ethical principles, which I am concerned about, if we decide to choose a particular course of action. There are certain rights involved, and this is what we must consider besides the scientific principles.

DR. PEARSON: To put this discussion into perspective, I will add that as recently as two weeks ago, the number of prenatal diagnoses or attempted prenatal diagnoses for the diagnosis of severe hemoglobinopathies reported throughout the world is a total of about 40. This involves the collective experience of centers in London, New Haven, Boston, San Francisco, and Philadelphia. So prenatal diagnosis is extremely investigational at the present time.

DR. SERJEANT: I wonder if I could ask the panelists to address the question of growth abnormality in children with SS disease. This is something most people accept. In fact, growth abnormalities extend into adult life. One of the most characteristic anthropometric differences in SS adults is the lack of obesity. As in today's case, lack of obesity occurred despite a fair appetite. Obesity does not occur despite a hearty appetite in some of our cases in Jamaica.

I wonder whether the panel would care to speculate about the possible mechanisms of the apparent inability of the SS patient to gain weight in the face of an apparently adequate caloric intake.

DR. POWARS: I would like to re-direct the question to Robert Penny. Dr. Penny is the pediatric endocrinologist for the Los Angeles Comprehensive Sickle Cell Center, and has been, and hopefully will be, addressing this problem for some years to come.

We have been very interested in this problem. I would like to remind you that Dr. Serjeant is the senior author of the report on 89 patients that does show that growth delay in sickle cell patients is not a permanent problem. By the time the patient reaches the third decade of life, or 20 years of age, he has grown to the size of his peer group or his siblings.

DR. PENNY: I think the essence of the question posed is, in the face of a presumed adequate nutritional "substrate," why isn't it translated into normal growth until a later time? The available information, which unfortunately is cross-sectional data, suggests that during

the period of childhood and adolescence, growth in these individuals tends to be suboptimal. I say, "tends to be suboptimal" because as a group you will find these individuals will fall within two standard deviations of the mean of normal. In other words, they are growing at the lower end of the normal growth curve. Available information also indicates that patients with sickle cell anemia have normal adult heights. These observations give rise to two questions. First, since adult normal height is defined as a mean with a variation around that mean, do these individuals achieve their full potential with regard to height? We cannot answer this question. Second, is there evidence that these subjects may have an impaired ability to translate "substrate" into growth? I would say from the clinical standpoint their suboptimal growth is consistent with this, but there are no hard data to substantiate this.

You could speculate that some or all of the tissues of sickle cell anemia subjects may be transiently impaired in their ability to convert growth hormone into its active forms, the somatomedins, or that these subjects may have a transient deficiency of a hormone or hormones necessary for optimal growth.

One reason for considering a growth hormone translation problem as a possible cause of less than optimal growth is based on the observation of differences in body composition between normal males and females subsequent to the onset of puberty. Normal males have more lean body mass (muscle and skeletal) than normal females. Conversely, normal females have more body fat than normal males.

Growth hormone has a significant influence on the growth of lean body mass (presumably androgens augment and/or complement responsiveness to growth hormone), and insulin has a significant influence on the growth of body fat. However, when the growth hormone concentrations found in men and women are compared, women are found to have the greater concentrations. Insulin concentrations found in normal men and women are comparable.

This paradox between body composition and growth hormone concentrations would be explainable if in the female, a factor restricts the action of growth hormone resulting in insulin action predominating, giving rise to a remarkable growth in body fat and much less growth in lean body mass. Such a factor is present in the female. It has been demonstrated that estrogens impair the conversion of growth hormone into somatomedins. Could the combination of chronic anemia and morbidity, associated with sickle cell anemia, act to impair growth hormone conversion to somatomedin? Because morbidity decreases with time in sickle cell anemia, the impairment could be transient.

Some preliminary data reported in the Journal of Pediatrics are consistent with a transient deficiency of hormones necessary for optimal growth. In a cross sectional group of sickle cell anemia subjects, we have found serum gonadotropin concentrations to be elevated during sexual development in the first decade of life, and to be normal during sexual development in the second decade of life. These findings are consistent with a possible transient deficiency of the sex steroid hormones.

I wish to emphasize that significant additional studies, particularly of longitudinal growth data, blood concentrations of sex steroids, and gonadal responsiveness to exogenous gonadotropins, are needed to validate the possibility that transient impairment in gonadal function occurs in some sickle cell anemia subjects.

A problem inherent in the evaluation of growth is that growing at the lower end of the growth curve may, in some sickle cell anemia subjects, represent their full growth potential. Such a growth pattern is common in individuals with delayed adolescence. Delayed adolescence results when the onset of puberty occurs at a chronological age which is later than the mean age, but which is within two standard deviations of the mean age observed for the normal population. The propensity is for delayed adolescence to occur in males. Our observations suggest that approximately 15 percent of a normal male population could be classified as such. In our experience, the subjects with sickle cell anemia who have been evaluated for impaired growth have been males, by and large. As yet we have no way to discern those sickle cell anemia subjects who are growing at the lower end of the growth curve for physiologic reasons, as in delayed adolescence, from those who are growing there because of occult pathologic reasons.

I believe that a longitudinal study in which growth data were obtained on normal Blacks and on sickle cell anemia subjects would contribute significantly to our understanding of growth in sickle cell anemia subjects.

DR. RANNEY: Is there a difference between growth in SS patients and, say, growth in thalassemic children or children with other anemias that are present at birth?

DR. PENNY: I really cannot say. We do not have many thalassemic children. The sickle cell patients by and large tend to do well during the first nine or ten years and then they start falling behind when you would expect the adolescent growth phase to occur. But, by and large, they never fall greater than two standard deviations behind in their growth.

Dr. Serjeant's data show sickle cell children's growth to be within two standard deviations of the mean for normal growth and Dr. Whitten's data indicate this with respect to height. Growth results from an increase in cell number and/or an increase in cell size, and height is a better index of increase in cell number than is weight.

Our biggest problem is that there is a tremendous variation in the normal range. This makes it difficult for us to look at a given individual's height and/or weight and say unequivocally that he or she is abnormal. If growth is less than 5 cm (or 2 inches) a year, that is abnormal. This is true of none of our patients. They are all growing at least at this minimum rate, and therefore, we are back to the question, are we observing merely normal variations? This we cannot say.

To put it more fundamentally, when you are considering growth you are talking about the genetic potential, the hormonal milieu, the nutrition available, and the time required to translate all of this into an increase in the size of the individual. Until methods are applied which will identify the specific mechanisms by which each of these contributes to growth, it is going to be difficult to tell which of these factors is at fault when growth is less than optimal.

DR. PEARSON: Dr. Whitten is in the audience, and perhaps he would like to address this point. The data he reported on in the American Journal of Diseases of Children 10 to 15 years ago showed that, when the growth rate of sickle cell anemic patients was compared to their non-SS peers, there was a marked shift to the left of their percentile performances.

DR. WHITTEN: That holds for our current data also.

DR. PEARSON: If you compare sickle cell patients with their peers, it is our impression from our own data that, although they may not be below the third percentile for height and weight, they are certainly in the 10th, 15th, or 20th percentile. As a group they segregate out very clearly as being small.

Perhaps we could pursue this further. We have two or three remarkably small, even dwarfed patients. They are more than two standard deviations below the means for their age in height and weight. These children have remarkably low hemoglobins. Whereas the usual patient with sickle cell disease has a hemoglobin of 7 or 8 grams percent, these children have 4 to 5 grams percent.

In some of these children we have begun a hypertransfusion program. This was followed by accelerated growth and growth spurts coincident with the increased hemoglobin level.

Dr. Friedman, you made two comments. You said that there is a low pO_2 in patients with sickle cell disease. I do not share your belief that retarded growth is entirely a pulmonary problem because it is present in infants with SS as well as in older patients. If it is a pulmonary infarctive process, it ought to be progressive.

DR. FRIEDMAN: I have been considering the absolute cost in terms of calories metabolized per day to perform cardiac and pulmonary work in the very small patient who has an extremely low hemoglobin. The situation is not all that dissimilar from the patient who has borderline or marginal cardiac compensation from some specific congenital cardiac malformation, another situation in which all the growth-retarding factors are not known. But surely cardiac and pulmonary work must play some role in growth retardation. However, this information is not available and would require complex metabolic balance studies to obtain. I suspect the calories metabolized per day in a child like that must be far in excess of the normal child.

DR. PEARSON: To respond further to Dr. Ranney's question, we do have some information from a retrospective comparison study on the management of thalassemia major. Treatment has changed in the last decade. A decade ago we maintained thalassemic children on a low transfusion program where the hemoglobin was allowed to drop to 5 to 6 grams before transfusions were given. Current therapy keeps hemoglobin levels above 9 or 10 grams/dl.

The growth patterns of a decade ago versus the growth patterns observed today in these children are quite different. The children ten years ago were dwarfed and retarded in height and weight. Today children maintained on hypertransfusions grow normally, at least for the first decade.

Are there other questions?

QUESTION: Dr. Powars, is there any information regarding bone marrow transplantation in sickle cell anemia?

DR. POWARS: Long bone or humeral head replacements have been performed to replace bone. I know of no substantive data regarding bone marrow transplantation done on any patients with sickle cell anemia. This procedure is being considered in several places, but I know of no patient on whom this has been done. Does anyone else?

DR. PEARSON: No, although it might be a feasible procedure, even with our present rudimentary experience in bone marrow transplantation. We know that one in four siblings with sickle cell anemia would statistically be suitable bone marrow donors. One would probably have to use toxic amounts of chemotherapy and radiation to transplant successfully. Immunosuppression would constitute a very real risk. The patient might well die. Since the natural history and the future course of sickle cell disease is clouded, many of us would be unwilling to take such a precipitous, irrevocable jump at this point.

DR. POWARS: We are now working with patients who are included in bone marrow transplant programs with aplastic anemia and unresponding acute leukemia. Many problems are encountered.

I think one might say the same thing about an issue Dr. Ranney addressed, namely, the use of regular blood transfusions in sickle cell disease. One can certainly render a patient with sickle cell disease asymptomatic by regular transfusions. But inexorably and inevitably, after 10 to 15 years of regular blood transfusions, the problem of iron deposition would shorten the patient's life span.

DR. MURRAY: I wonder if I could ask Dr. Ranney to comment on the resources necessary to support patients in hypertransfusion programs. This is a question that I have been asked many times. Frankly, I do not know what the blood bank capacities are, nationwide. In other words, what proportion of sickle cell patients might possibly be able to avail themselves of hypertransfusion programs, say, during pregnancy or at other times?

DR. RANNEY: I do not think there has ever been a limitation on availability of blood for patients with sickle cell anemia during pregnancy, particularly in this country. Many clinics have transfused rather liberally in the last trimester of pregnancy. Of course, this statement might not apply to other areas of the world.

The limitation for hypertransfusion for patients with sickle cell disease was alluded to by Dr. Pearson. The symptoms of sickling are ameliorated, but after 15 to 16 years of transfusions, overload with heart and liver disease becomes manifest. As a result we have been very conservative about using transfusions. Some hematologists use transfusions more freely than others, and some will use them for a child who does not seem to be doing well in breaking a cycle of recurrent crises.

There are circumstances in which I have transfused patients with sickle cell disease for eight months or a year with the hope that the person who was leaving school because of illness and pain could get back to school, with fewer crises and more confidence in the future. Sometimes it seemed to work. But there are no controls because we never know how that child would have done in a given year if he had not received transfusions.

I am very dubious about transfusions lasting longer than eight months to a year because of the long-term problems of iron overload. But every once in a while an SS patient has a bad year and this procedure may be tried.

DR. POWARS: I would like to add that we do have patients we are forced to transfuse from early infancy. This includes youngsters with Blackfan Diamond syndrome and children with homozygous beta-thalassemia. When you begin transfusions at four, five, or six months of life, you must bring the child into the hospital every three to four weeks involving the whole needle scene, the misses, the repeats, and the problems with the bank blood. After about four or five years, you might have problems with cross-matching because of the increased level of antibodies. With all of these problems you

begin to appreciate the implications and consequences of long-term transfusion programs. In addition, this type of therapy has far-reaching psychological effects and tends to constantly remind the child that he has a major illness; there is constant reinforcement that he is not normal and is isolated from other children.

DR. PEARSON: I think it is important to emphasize that the child with sickle cell disease is well most of the time. It is only the periodic crises and complications that make him realize he is sick. Chronic transfusions probably would ultimately cause many more problems than they would prevent. However, there is convincing evidence that children who have had strokes probably warrant a prolonged transfusion program. Data from Philadelphia show convincingly that cerebral vascular abnormalities can be reversed for a year or so by a chronic transfusion program. I think strokes constitute a clear indication for a chronic transfusion program.

QUESTION: Have there been any studies on the nutritional aspects of SS patients in terms of the calories provided against those that are actually ingested, and the assimilation of these calories?

DR. PEARSON: This question again concerns whether there is malabsorption or malutilization of ingested calories in sickle cell disease. I will ask any of the panel members to comment.

DR. POWARS: I know of no studies that could really demonstrate in a balanced way how well a three-year-old youngster absorbs the calories delivered and how well he utilizes them.

There are classic statements by Dr. Konotey-Ahulu indicating that, as populations of people are better fed, with an upgrading of general nutrition, sickle cell anemia patients in those populations seem to do better. We all believe that if a patient is well-fed and has a good nutritional balance, he will do better on the whole. But I do not know of any controlled studies that show this.

DR. FRIEDMAN: That is really what I was referring to before. The SS patient's problem is not just malabsorption or malnutrition. The patient may be appropriately utilizing calories but the metabolic demands may be far in excess by virtue of the patient's own compensatory mechanisms.

DR. POWARS: One thing that may be useful on a day-by-day basis with the youngsters with sickle cell anemia is, instead of offering them three meals a day, we have found that five or six equally divided meals a day are better. These should provide important protein and good nutrition. Because these youngsters cannot eat quite as much as their peers, we divide their food and encourage snacks which have real food value in them.

DR. FRIEDMAN: There are other nutritional considerations which concern prenatal nutrition of the fetus. I think this area would also have to be studied as part and parcel of the overall nutrition question.

QUESTION: Could you enlighten us on the mechanism of enuresis?

DR. POWARS: The enuresis problem is very real. If you go to camp with youngsters with sickle cell anemia who use sleeping bags for eight days, you really will begin to appreciate this.

In my discussion with Dr. Ranney I invoked an overly simplistic point of view. If you watch children as they sleep, the little ones sleep so hard you could drop pans around them without waking them up. They will sleep right through anything, including urination.

It seems to us, without hard data at all, that what happens is that as the child reaches 8, 9, 10, and 11 years with his increased urinary output, he begins to wake up and his enuresis changes to nocturia. He gets up and goes to the bathroom instead of wetting the bed.

We have performed innumerable studies including IVP's and renal concentration studies, but to no avail. Several types of medications have been tried; none of them work. Eventually the youngsters begin to get up. We see that at camp particularly where the children get up about twice a night.

DR. RANNEY: If you are right, Dr. Powars, then adult patients should rather regularly have nocturia.

DR. POWARS: Don't they? I mean, those over 40?

DR. PEARSON: Or larger bladders.

DR. RANNEY: Or larger bladders. I am not sure that I remember nocturia as a frequent complaint among SS patients. One who routinely gets up once per night may not regard this as a symptom of sickle cell disease unless he were specifically questioned about it. But in other anemias the specific gravity will be at least transiently affixed.

What about the children with thalassemia? Do they have enuresis, Dr. Pearson?

DR. PEARSON: In my experience, no.

DR. RANNEY: But they do not concentrate urine that well in childhood, or do they?

DR. PEARSON: They certainly can concentrate 1:020 or so.

QUESTION: Could I just pursue that? If one believes SS patients are more prone to enuresis than controls, then you have to postulate that either they sleep more soundly or they are not subject to the same parental pressures, or their bladders are less sensitive. Would you care to choose?

DR. PEARSON: Another possibility would be that they make more urine.

DR. FRIEDMAN: SS patients clearly make more urine.

DR. RANNEY: They are making more urine, Dr. Powars, would you agree?

DR. POWARS: Yes.

QUESTION: If a normal person gets up in the middle of the night to empty his bladder, why should not an SS patient do that several times during the night?

DR. POWARS: Enuresis in childhood is a very common problem, far more common than most people would want to believe. It is more common in the male youngster of five and six than in the female. I would be hard-pressed to try to really tell you how common enuresis is, but I would guess that as many as 25 percent of all children up to age five or six wet the bed every so often. It is a very common problem.

QUESTION: But you believe there is a real difference? You believe enuresis is increased in SS patients?

DR. POWARS: Yes, I do, but I believe this without any hard data. It is just based on my experience of getting up at night with sickle cell patients at camp.

DR. PEARSON: As the chairperson of the Pediatric Grand Rounds I would like to thank both the panelists and our audience for such a stimulating and enlightening session. I am delighted at the way the individual presentations and the discussion have complemented each other. Thank you very much.

formal presentation

THE NEED FOR AND AN APPROACH TO PARENT EDUCATION

Charles Whitten, M.D.

I became interested in the problem of educating individuals with sickle cell anemia and their families in 1967. At that time a medical student, Joyce Essien (she has since received her medical degree), and I interviewed 50 adults with sickle cell anemia and 50 parents of children with sickle cell anemia. We were exploring, through taped interviews, their experiences with sickle cell anemia, their level of information, and their attitudes, feelings, and adjustment.

We were appalled at how little these parents and adults, some of whom had had sickle cell anemia for 20 to 30 years, knew about the disease. Their ability to cope with the disease was at an unacceptable level and some had had disastrous marital, work, and job-seeking experiences.

Our analysis of the causative factors of this situation indicated that the major problem was that, by and large, no one had attempted to inform the patients and parents about the disease and how they might learn to cope with it. These were patients who had been managed by private physicians in Detroit or treated as outpatients and inpatients in our major hospitals, including university-affiliated hospitals.

On two occasions in 1971 we videotaped unrehearsed group discussions on sickle cell anemia. The first group consisted primarily of adults with sickle cell anemia and the second group was largely composed of parents of children with sickle cell anemia. No health professionals were in either group and the participants were simply asked to talk about the disease.

I want to show a few minutes of one of the tapes. *(The following is a transcript of the portion of the videotape shown at the conference.)*

A PARENT: And the shocking thing is that we did not know the gene was in the family, or anything about the situation until the fourth child was born, and he was diagnosed when he was two years old.

ANOTHER PARENT: My experiences with sickle cell anemia make this discussion very interesting to me. So many times you take your child to the hospital and they never explain anything to you. They just let her lay up there and give her some blood if she needs it, and after a few days they tell you, "Well, she can go home." And if you say to a doctor, "Well, she has the trait of sickle cell anemia," he will say, "Oh, is that so?" And then they never explain anything to you.

So this is why I was so interested in getting over here, because I wanted to know more about the disease. My husband and I, neither of us had the trait or the disease but my child had the anemia. Then there are two other children by my husband and neither of them even have the trait.

(End of excerpt)

I would like to focus on two aspects of that very brief segment of a one and one-half hour discussion. The first mother was bitter about not having been made aware of her potential for having a child with sickle cell anemia. The second mother has had a child with sickle cell anemia for seven or eight years, but states that neither she nor her husband has the trait. Also, there were some criticisms of physicians. This discussion is just one of many expressions of parental concern over being uninformed and of criticisms of physicians for their failure to discuss the disease in depth with them.

In 1973, stimulated by the 1967 study and the videotaped discussions, we began designing a program for a comprehensive sickle cell center. It seemed unlikely to us that we would be able to address the problem of patient education on an ongoing basis through the house-staff. I was also looking for some mechanism for maintaining continuity of care in a hospital where a rotating house-staff provides the major part of the care. So we decided to use nurse practitioners as the primary care providers and patient-parent educators, using the house-staff and staff physician as consultants.

To systematize the educational activities of the nurse practitioners, we developed an educational program with three major elements for parents. First, we assess the parents' (usually

the mother's) knowledge, attitudes, feelings, and behavior through an audiotaped open-ended interview. We use a 45-item questionnaire as an interview guide. Then we have the parents view an audio-slide presentation that we developed called, "The Sickle Cell Story." In 15 minutes it gives an overview of sickle cell anemia.

Finally, the nurse practitioner conducts a series of one-on-one educational sessions with the parent(s), covering genetics, pathophysiology, symptoms, mortality, treatment, home management, and adjustment. We have a form for the nurse practitioner to use to indicate the areas covered during each visit, and a rating of comprehension.

We have taped and analyzed over 125 of the needs assessments conducted during 1974-1975. I call them "needs assessments" because we are ascertaining parental knowledge, feelings, attitudes, and behavior, and using that information to determine the need and content for the ongoing educational sessions.

The needs assessment indicated that there had been little improvement in overall parent education since 1969. I have selected a few of the 45 items to highlight areas of inadequate information. Also, I will present anecdotal evidence that misconceptions have had an adverse influence on behavior and/or attitudes. The vast majority of these mothers have had a child with sickle cell anemia for at least two years, and some for as long as 10 or 15 years.

When asked questions about heredity, 82 percent knew that sickle cell anemia is a hereditary disease. But 27 percent of this group did not know that both parents are involved. A few mothers indicated that there had been "cross-accusations" between parents as to which parent was responsible for the child having sickle cell anemia.

One mother indicated that she had been ostracized by the father's side of the family because she had brought this "bad gene" into the family. Later, when a family member on the father's side of the family had a child with sickle cell anemia, the family tried to establish a relationship, but she rejected them.

Only 40 percent of these 125 parents could give a satisfactory definition of anemia. This has some adverse implications, too, as I will mention in a moment. Forty-five percent could not give a satisfactory definition of sickle cell anemia.

Thirty percent viewed crises in a non-medical sense, that is, as being an emergency requiring some immediate attention. I think one thing we could do for patients, parents, and families that would be most helpful, would be to drop the use of the term "crisis." I think it is going to be extremely difficult for us to get parents to understand our medical definition of "crisis."

Again, an anecdote. I know of a father whose behavior exemplifies the influence of the lay definition of crises. He had a telephone installed in his taxicab so that he could be reached directly at any time by his family when his 14-year-old boy had pain. He would leave his route, pick up the child, and immediately carry him to the hospital. That is the way he was functioning when he came to the clinic. He also had associated frequent episodes of severe pain with early death. "Doctor," he said, "he just cannot live if he keeps having these severe crises."

Only 45 percent could accurately differentiate between sickle cell trait and sickle cell anemia. Many thought that because they had the trait, they would have some problems, for example, pain, which would not be as severe as in sickle cell anemia.

Fifty percent were unable to provide a satisfactory explanation for pain in sickle cell anemia. Their lack of knowledge as to why pain occurs, and what can be done about it, had contributed to their low opinion of the ability and interest of some of the physicians who had provided care for them in the past.

Approximately 50 percent were under the impression that individuals with sickle cell anemia do not live to be adults. This had had drastic effects on how some of them related to their children. I would like to cite another bit of evidence which indicates that parents have inaccurate information about the lifespan of a sickle cell anemia patient.

Several years ago, Bill Cosby produced a 90-minute television drama entitled, "To All My Friends on Shore." The plot was based upon

the family's reactions to the discovery that their 12-year-old child had sickle cell anemia. They had been told that he would die soon, despite the absence of any severe or life-threatening complications.

We interviewed 50 parents who had children with sickle cell anemia, but who were not attending our clinic, to see whether they and their children watched the show and how they responded to it. We found that about a quarter of those who watched the show were deeply upset about the way it was handled. Also, their children were upset. But they were not knowledgeable enough about life expectancy to tell their children that this was just a drama. In effect, they were so uncertain that they dealt with the disease from a fatalistic or religious point of view. For example, one parent reported that she told her child, "You are going to live as long as you are supposed to, and we are going to try to be happy as long as we live."

Back to the needs assessment: 62 percent had had some thoughts about whether their children might die when they had been ill. In the vast majority of instances, this feeling arose over a complication which no physician would feel threatened a child's life, such as an episode of pain. The parents have been told that the lifespan is shortened in sickle cell anemia, but no one had told them under what circumstances children die. So it should not be surprising to learn that parents' anxieties were ill-founded at times, or that none of these parents indicated they had ever discussed their apprehension or uncertainties with a doctor.

We asked, "Are there any diets or any foods that will decrease the frequency of problems in sickle cell anemia, particularly pain?" Sixty-five percent answered, "Yes!" Ninety percent could not give an explanation for anemia in sickle cell anemia. This and the previous question are related, because for the layman, iron deficiency is frequently assumed to be the cause of anemia. In keeping with this, there were certain foods, particularly those with a high iron content, that parents thought these children should have, and some parents have placed great emphasis on feeding these foods to their children.

After about two years' experience in our center with providing educational services based upon a needs assessment, we feel we have been reasonably successful. We have collected data at three months and six months, respectively, after the first visit. These data indicate improvement; however, there are at least four problems in implementation that have an impact on overall effectiveness.

First, it is difficult to maintain up-to-date awareness of each patient's educational status. We do not have a satisfactory recordkeeping system and possibly not enough time to record sufficient data about patient comprehension. Each nurse practitioner has approximately 125 patients.

Second, it has been difficult to get parents to come in for educational sessions. We have scheduled sessions in the evenings to make them convenient for fathers, but the sessions were so poorly attended that we discontinued them.

Third, we are not faced with the same time problem in the clinic, with the nurse practitioner trying to schedule time for providing education. A shortage of time is one of the barriers preventing physicians from providing education. Not infrequently, the nurse practitioners have planned an educational-counseling session as part of a routine check-up and have not had the time to render the service because three or four patients come in who need immediate medical care.

Finally, we seldom get fathers in for educational sessions. Obviously, they need to have accurate information on sickle cell anemia, as well as other members of the family.

The need for some changes in our educational program was further prompted by the fact that, although the use of nurse practitioners might be the answer to the educational need of parents attending specialized clinics, only a few patients in this country will be receiving primary care from nurse practitioners in the near future. The vast majority of individuals with sickle cell anemia obtain, and will continue to obtain, their medical care from private physicians. An educational approach that is not replicative in a physician's office is not going to meet the needs of the vast majority of parents of children with sickle cell anemia. But neither is the development of educational approaches dependent upon physician implementation likely to be helpful at

this time. Physicians, by and large, do not have the time, the interest, or the motivation to do an acceptable job as patient educators.

The training aspect is worthy of further comment. Very few of our medical school curricula contain anything on the techniques or need for educating patients. It appears as though we have assumed that physicians, through their training, are automatically capable of satisfactorily educating their patients, or that patient education is not important, or not the responsibility of the physician. The advisability of shifting this responsibility to nurse practitioners has had further merit since it is too costly to have physicians performing this task when others can do it as effectively and more economically.

Although in our program we have not utilized physicians as educators, using nurse practitioners as educators on a large scale is not possible since few nurse practitioners provide primary care for sickle cell patients. Thus it seemed worthwhile to attempt to meet the educational needs of sickle cell parents primarily through a self-education approach. In effect, through self-education instruments we could give the parents the responsibility for the control over their education. This consideration led us to develop a self-instructional home study kit which we have called "The Sickle Cell Home Study Kit for Parents." The educational objectives for the home study kit are that parents will be able to satisfactorily explain:

- What sickle cell anemia is.
- What sickle cell trait is.
- How children get sickle cell anemia.
- What symptoms occur and when.
- What the physician can do to treat sickle cell anemia.
- What the overall outlook is for a child with sickle cell anemia.
- What constitutes realistic goals for children with sickle cell anemia with respect to careers, marriage, and reproduction.
- How to cope with sickle cell anemia.

The kit contains six instructional elements. The first is a 44-page booklet entitled "Sickle Cell Basics" in which we cover information about the disease and about coping with it. The format consists of bits of information followed by a request to turn to a page in the booklet, "Test Your Knowledge," which contains questions and answers on the information just covered. We have provided at least one graphic (total of 66) for each point discussed in "Sickle Cell Basics."

The following figures give you a picture of the type of information in the booklet and how it is illustrated. Figure 36 shows sickle cells plugging a blood vessel and Figure 37 indicates that normal red blood cells have a lifespan of 120 days and sickle cells only live up to 30 days. These figures accompany a discussion of why individuals with sickle cells have health problems.

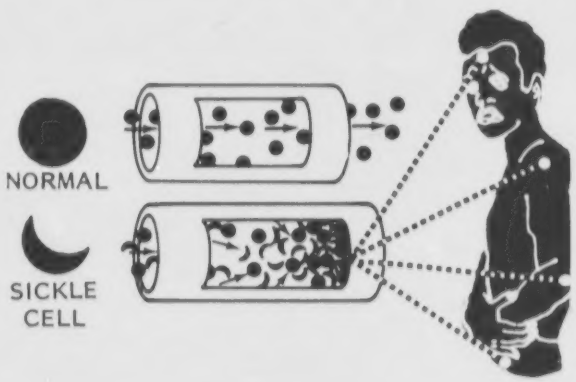


Figure 36. Sickle cells shown plugging a blood vessel.

The booklet covers sixteen medical problems that can occur because of sickle cell anemia. Each is schematically illustrated. For example, there is one on pain (Figure 38), one on gallstones (Figure 39), one on strokes (Figure 40), one on splenic sequestration (Figure 41)--Few parents know where the spleen is. We have a sketch of the chest and abdomen with a normal size spleen containing red blood cells and a second panel with an enlarged spleen from engorgement with red blood cells symbolically showing the outflow tract plugged with sickle cells.

We have included in the booklet all the health problems that are related to sickle cell anemia. Is this advisable? There is an obvious risk of frightening individuals with all this

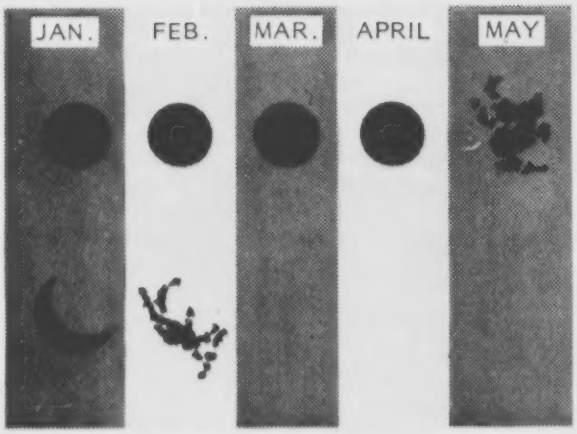


Figure 37. A normal red blood cell lives for 120 days, while a sickle cell has a lifespan of only 30 days.

information. On the other hand, we have to balance this risk with the fact that some parents are very angry when a child has a symptom or complication that they were not aware could occur.

We have decided we would prefer to be guilty of the former rather than the latter, and have included all of the problems. However, we stress the variability of the disease from child to child and the low probability of occurrence of some of the more severe complications.

We then cover sickle cell trait and some of the related health issues. Figure 42 indicates how we deal with the question of the safety of air travel. The top of the figure represents an altitude of 30,000 feet with widely spaced "bubbles" of oxygen depicting the thinness of the air. Within the jet airliner the bubbles are as close together as they are at 5,000 feet. For this reason, no difficulty is experienced in traveling in jet airliners. There is a second small plane at 10,000 feet in which the bubbles are more widely spaced than at 5,000 feet, and they are the same distance within and without the plane. This indicates that in unpressurized small planes, traveling above about 8,000 feet, a person with sickle cell trait could have sickling occurring leading to intravascular plugging.

The next area covered in "Sickle Cell Basics" is coping with the disease. The format consists of a statement of the problem, a description of what the parents can do about it, and a graphic illustrating either the problem, the effects of the problem, or an approach to resolution of the problem. For example, one problem is stated thus: "You and the child's other parent might not agree on how to raise the child. It becomes very confusing and difficult for the child when the parents have different ideas." Figure 43 illustrates this point. Figure 44 is used for the problem of teasing, and Figure 45 features Sammy Davis, Jr., showing that there are famous people who are small in size. This is used to relate to the negative effect that small stature can have on the self-esteem of adolescents with sickle cell anemia.

In covering the genetics of sickle cell anemia, we take the parents back to the union of the sperm and egg, and the fact that we have different types of hemoglobin because of the message (gene) in the sperm and egg, just as messages are there for other characteristics that make us like our parents (see Figure 46).

The booklet also discusses the types of children trait-normal couples and trait-trait parents can have, and what happens if one parent has sickle cell anemia. This is a very important factor to cover because, as I indicated earlier, in responding to the needs assessment questionnaire, most parents stated, "Yes, sickle cell disease is hereditary and, yes, both parents must have the trait." But when asked, "What do you think about your child, who has sickle cell anemia, eventually having children?" The response was frequently, "Oh, no." If asked "Why not?", the typical response was "Because I don't want him to have children with sickle cell anemia," forgetting or not being able to translate this information into the fact that the other parent would also have to provide the sickle cell gene.

The kit contains a cassette tape and film strips. The tape is a 90-minute recording of a simulated counseling session which I conduct for two parents who have just learned that their child has sickle cell anemia. The parents make comments and ask questions for me to answer.

Figure 38. Pain

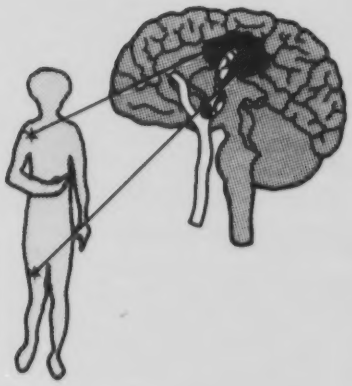


Figure 40. Strokes

Figure 39. Gallstones

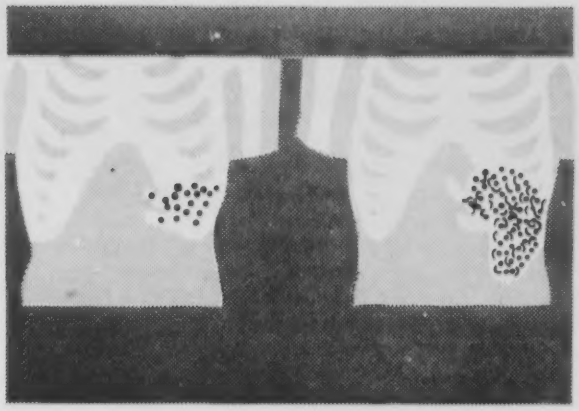


Figure 41. Splenic sequestration (shown on the right) in which the outflow tract of the spleen is plugged with sickle cells resulting in the spleen's engorgement with red blood cells.

Figures 38-41. These drawings illustrate various medical problems that can result as a consequence of sickle cell anemia.

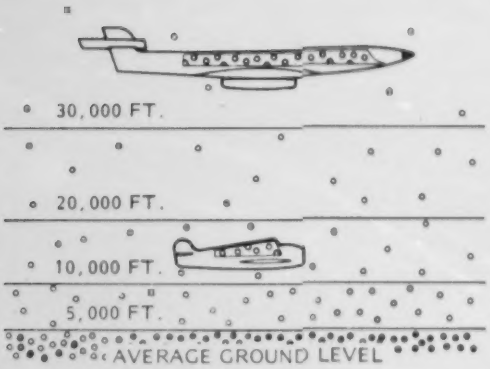


Figure 42. Illustration of the safety of air travel for the patient with sickle cell anemia.

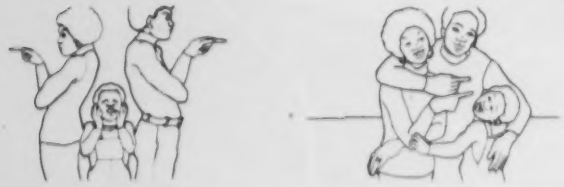


Figure 43. These sketches indicate that parental differences over how to raise their child are very confusing for the youngster.

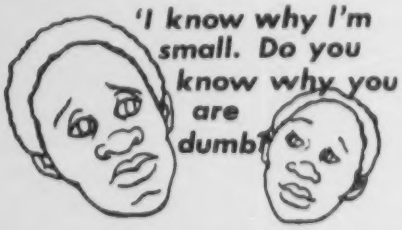


Figure 44. A child with sickle cell anemia may have to deal with the problem of teasing due to his relatively small stature.

During the session I cover all of the material in "Sickle Cell Basics." While discussing the various points, the parents are instructed to view illustrations on three film strips. The illustrations are those used in "Sickle Cell Basics." From time to time a narrator asks a question and requests the parents to stop the tape and try to answer the question. When they turn to start the tape again, the narrator gives the answer.

There is a manual on coping with sickle cell disease, developed under my direction a couple of years ago by the National Association for Sickle Cell Disease, Inc. It is entitled, "How To Help Your Child Take It in Stride."

Figure 45. A picture of Sammy Davis, Jr., is used to show sickle cell patients that there are famous people who are small in size.

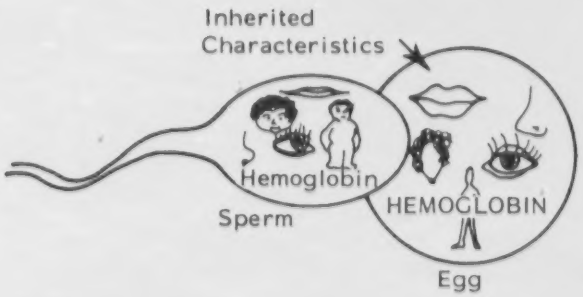


Figure 46. Inherited characteristics result from the types of messages (genes) contained in the sperm and the egg. The type of hemoglobin someone has is an inherited characteristic.

We believe there is a minimum body of information that parents need to acquire, not only to aid them in coping and in having appropriate attitudes and behavior toward sickle cell disease, but also to enable them to be more comfortable when discussing the disease with physicians and to make those discussions more meaningful to them.

For example, many of our patients cannot discuss or are very uncomfortable in discussing sickle cell anemia with a physician. They do not know the concepts or the meaning of various terms we use. For example, they do not know what hemoglobin is or what it does, or the significance of the various values that are obtained. Yet we determine the child's hemoglobin concentration frequently and mention it to the parents or they overhear it in discussions in the clinic. This type of information gap is covered by the questions.

The information is put into question form. In effect, we are saying that there are certain questions that parents should be able to answer. Questions such as: What is sickle cell anemia? What is sickle cell trait? What can doctors do when a child with sickle cell anemia has pain? How much hemoglobin does the child with sickle cell anemia usually have? To help the parents learn to answer these questions, we put each question on a flash card with the answer on the back of the card. There are 33 cards.

Incidentally, the answers are simple, direct, and brief. For example, for the question, "What can the doctor do when a person with sickle cell anemia has pain?", the answer is "The doctor can relieve pain with drugs, but he cannot remove the cause of the pain." We sometimes recommend a group activity with the cards; for example, one family member can read a question and the others can attempt to answer it.

The kit also contains a set of plastic dice with removable labels. These are designed to illustrate the element of chance in the inheritance of sickle cell trait and anemia. The user can construct parents who have all normal hemoglobin, sickle cell trait, or sickle cell anemia. Each roll of the dice yields a child the selected parents could have. A tally sheet is provided to record the result of each roll. Through this exercise they can learn what can happen in families, depending upon the type or types of hemoglobin the parents have.

The final item in the kit is a crossword puzzle which embodies the 33 concepts on the flash cards. An answer sheet is provided. You will note that there is instructional variety in the kit. There is expository typewritten material, self-instructional written material, an audiovisual unit, an exercise for group participation, and two games. The use of a variety of instructional modes is an attempt to appeal to a spectrum of interest and educational levels.

We, of course, recognize that everyone will not be interested in using everything in the kit, so we have purposely covered the most important material by several modes. Even those who elect to use just one or two of the elements can acquire some useful information. On the other hand, those who complete the kit will probably benefit from the reinforcement inherent in repetition.

In our unit, I plan to administer a pre- and post-test, both for evaluational and instructional purposes. The test will indicate the effectiveness of the kit in transmitting information. In addition, each parent's pre- and post-test will be used to guide the nurse practitioner's ongoing educational efforts with the parent.

It will not be very difficult to assess the value of the kit in terms of acquisition of information. What is going to be very difficult, and what is vitally needed, is to determine the extent to which it is beneficial for parents to be better informed about sickle cell anemia. How much positive impact does being better informed have on feelings, attitudes, behavior, and morbidity? The latter is a particularly vital aspect to consider. Is there a relationship between the quality of the parents' information and the degree of severity of the effects of the disease on the child?

These experiences in sickle cell anemia are not unique in dealing with chronic diseases. There have been published reports on rheumatic fever, diabetes, and cystic fibrosis which indicate that there are similar problems in getting parents educated so they are in a better position to cope with these chronic illnesses, and in a better position to achieve what all of us would consider to be the basic goal of our comprehensive care: that is, until we have a cure for diseases such as sickle cell anemia, we are enabling individuals to live high-quality lives, compromised only by the unalterable aspects of the disease.

DR. BOWMAN: Could you try the same questionnaire in the beginning on the physicians? I think quite a few of the physicians would also have flunked, as did the patients.

DR. WHITTEN: I think that is a major problem. And indeed two factors emerge from discussions with patients. The first is, if you ask them to identify the source of the information they have about sickle cell and sickle cell trait, only 45 percent will indicate a physician. Second, if you ask, "Where did you get your impression about food being helpful?" -- and some of the other misinformation, for example, concerning lifespan -- a high percentage will frequently identify the physician.

DR. BOWMAN: The second question which is often asked, and which I often ask myself is: "How much should we really expect patients and/or parents to know about a particular disease? Should we not individualize more? Can we give the same information to all patients and to all parents?"

A personal thing -- about three years ago when I had a coronary, which fortunately was mild, I thought to myself that physicians really are at a disadvantage, in a way, in that we know all of the ramifications, all of the horrible things that could happen. And most of these horrible things are not going to come to pass, but there you are, there is nothing you can do about it.

But what about the patient? I mean, it is necessary, for example, for a child who is 18 years of age to know that he or she may have a stroke? At that time he has maybe passed that point, because only a small percentage of patients have strokes -- or all of the other things that might happen. How far do we go? And is it not possible in our education efforts that our patients may get what most of us physicians have gotten in medical school, so-called medical students' diseases?

DR. WHITTEN: That is unquestionably a problem. And it seems to me, rather than making prejudgments about what information should not be included, that we need to include everything, and then ascertain what the reactions are, and see if we can then develop some criteria for selecting what information should be covered. Currently, we simply do not have the information necessary to determine the best approach.

On the other hand, several experiences lead me to believe that it is going to be very difficult to arrive at an answer, because individuals will tell you that they are frightened, apprehensive, and do not want to hear everything about the disease. Then when something happens later for which they were not aware of the potential, they are critical of the physician for not having informed them.

What our approach is going to be is to make the information available to them and get some reactions from them, as we did with the pretest with some of this material, to find out whether or not they indeed wished to know everything. We found the vast majority we pretested did want to know all of the possible manifestations.

Of course, we are very careful in emphasizing in the written material and on the tape that we do not anticipate everyone will have everything, and some of the worst complications have a very low incidence.

QUESTION: Often I think it is the fear of the unknown that is frightening. I think most parents would like to know what can happen so they can approach the situation in a more informed way.

DR. WHITTEN: That is what we have heard from the vast majority of our parents also.

DR. MURRAY: You suggested we get rid of the word "crisis." How about getting rid of the term "sickle cell trait" and substitute "sickle cell gene carrier?" Might that not be helpful?

DR. WHITTEN: I have not seen the term "sickle cell trait" to be a problem. I think the concept of sickle cell trait has been a problem. Physicians call it a mild disease, and so forth. But it is a question of whether or not a carrier can have problems. Dr. Murray, what does that term "carrier" mean to a lay person? Could a carrier have problems?

DR. MURRAY: A carrier of any gene can have problems.

DR. WHITTEN: It does not really help, then.

DR. MURRAY: But the term "trait" has a specific meaning in our language, just as "crisis" has a particular meaning in our language.

DR. WHITTEN: I would agree that this is something we need to consider, but I personally have not seen the term itself to be the problem. But it is certainly open for discussion, I am sure.

QUESTION: Dr. Whitten, speaking of education, some years ago many of the patients faced quite a dilemma in seeking employment because of the way in which employers perceived the sickle cell patient. I am wondering if that kind of thing has changed any, and whether anybody is trying to get information on those patients?

DR. WHITTEN: Employment is still a major problem, and there are a number of reasons for it.

Incidentally, in our Children's Hospital, where our Comprehensive Center is located and where I have been for years, we have a career development program. One of the young men, an x-ray technologist who we had assisted, was denied permanent employment at the hospital because he has sickle cell anemia. He is employed there now, but on a temporary basis.

Part of the problem stems from the criteria for eligibility for pension plans and the concerns over the possibility of individuals with chronic diseases claiming aggravation of their illness, thereby becoming eligible for long-term workmen's compensation benefits.

mini-symposia

CLINICAL MANAGEMENT

Helen Ranney, M.D.
Donald R. Harkness, M.D.
Robert S. Rhodes, M.D.

IMPAIRING THE SWITCH FROM THE GAMMA CHAINS OF HEMOGLOBIN AFTER THE BETA CHAINS OF A.

Helen Ranney, M.D.

The occurrence of fetal hemoglobin in patients with sickle cell anemia, together with the in vitro evidence that fetal hemoglobin impairs sickling, have long suggested that a potential therapeutic maneuver in sickle cell anemia might be found if the switch from fetal to adult hemoglobin synthesis could be prevented. The controls, genetic and environmental, involved in the switch from fetal to adult hemoglobin production during normal human development have defied ready delineation.

Blood samples from fetuses of 8 weeks gestational age contain hemoglobin F, together with variable amounts of hemoglobins Gower 1 and 2 and hemoglobin Portland. Hemoglobin Gower 2 contains alpha and epsilon chains; Gower 1 may be epsilon 4 or zeta 2, epsilon 2. Hemoglobin Portland appears to be most likely gamma 2, zeta 2 (see Table 2). The order of appearance of the alpha, beta, zeta, and epsilon chains is uncertain although the first chain synthesized is probably the epsilon chain, followed by the alpha and zeta chains, and finally the gamma and beta chains. Gamma chains are present in two classes, one with glycine 136 and the other with alanine at that position. The synthesis of alpha chains, once established, continues throughout fetal development into adult life. The production of epsilon chains ceases before the 8th week of gestation when gamma chain synthesis is fully activated. Hemoglobin F is therefore the major hemoglobin from the 8th week of intrauterine life.

Table 2. Human Hemoglobins During Development

Gestational Age	Hb	Gross Structure
8 Weeks or Less	F	$\alpha_2\gamma_2$
	Gower 1	$?^{\varepsilon}{}_4$ or $\zeta_2\varepsilon_2$
	Gower 2	$\alpha_2\varepsilon_2$
	Portland	$\gamma_2\zeta_2$ (?)
Probable Order of Appearance = ε, α, ζ, γ, β		
After 8 Weeks	F	$\alpha_2\gamma_2$
	A	$\alpha_2\beta_2$

Beta chain synthesis begins at a low level by the 8th week of intrauterine life, and hemoglobin A is present as 8 percent to 10 percent of the total hemoglobin from about the 8th to the 34th week of gestation. After 34 weeks, beta chain synthesis is more active and by birth nearly equal amounts of gamma and beta chains are being produced. By the end of the first year of life, hemoglobin F has usually fallen to less than 5 percent, and reaches its adult value of less than 1 percent during the first few years of life. The timing of the switch from gamma to beta chain synthesis depends on gestational age and is unrelated to birth or to known environmental factors.

The sites of erythropoiesis change during fetal development. The first red cells produced are in the primitive mesenchyme, which may be the site of embryonic hemoglobin production. After six weeks, erythropoiesis is established in the liver and spleen, and the bone marrow becomes the site of red cell production in the intrauterine life. Hepatic and splenic erythropoiesis does not completely cease until just after birth. The relative amounts of hemoglobin F and A have been shown to be the same in different organs of erythropoiesis during different phases of fetal development. The switch from fetal to adult hemoglobin is synchronized throughout the fetus and there is no evidence that different hemoglobins are produced at specific sites.

Hemoglobin F can be identified in cells by the older acid-elution techniques and the recent, more sensitive fluorescent anti-hemoglobin F antibody technique. By both techniques the presence of both hemoglobins A and F can be demonstrated in most cells at the time of birth. During maturation the number of cells containing hemoglobin F gradually decreases. While nothing is known about the number of zeta or epsilon chain genes or their chromosomal relationships

to the beta-gamma loci, close linkages between the later appearing non-alpha chains, that is, gamma, beta, and delta, have been demonstrated. The order of the genes appears to be G (glycine) gamma, and A (alanine) gamma, delta, and beta.

Huisman and Schroeder have suggested that there are four gamma chain loci with a major and minor locus for both the G gamma and A gamma chains. Recent estimates of the number of gamma genes by hybridization techniques are compatible with that model. Lanyon and his associates recently demonstrated differences in RNA isolated from nuclei of adult and fetal tissues, suggesting that translational control is not the major mechanism in the expression of gamma globin genes in fetal as compared with adult life.

Hemoglobin F in normal adults, according to the studies of Boyer and of Wood, is found in a small proportion of red cells. The percentages have ranged from about less than 1 percent to about 8 percent of the red cells. The observed differences probably represent differences in the sensitivity of methods used. The hemoglobin F of adults has a different glycine to alanine ratio than that of newborn infants. In adults, the glycine to alanine ratio is 2 to 3, while in newborn infants it is 3 to 1. This has been interpreted to suggest that one of the gamma chain glycine loci is completely inactive in adults.

There are two broad classes of hereditary conditions in which hemoglobin F synthesis persists beyond the neonatal period (see Table 3): 1) congenital hemolytic anemias; and 2) the heterogeneous group of conditions which have the general title of "hereditary persistence of hemoglobin F." Significant amounts of hemoglobin F are in general found in only two congenital hemolytic anemias, sickle cell anemia and beta thalassemia. In both disorders, the hemoglobin F is heterogeneously distributed among the red cells. In sickle cell anemia, the amounts are usually in the 5 percent to 10 percent range, and except in the Saudi Arabian group of sicklers, rarely rise above 10 percent of the total hemoglobin. In the Saudi Arabians, the amounts range between 10 percent and 30 percent. In homozygous beta thalassemia, hemoglobin F ranges between 10 percent and 100 percent. In sickle cell anemia, there is clear evidence from earlier studies that the cells which contain predominantly hemoglobin F have a considerably longer life span than those containing hemoglobin S. In most of the types of hereditary persistence of fetal hemoglobin, hemoglobin F is found in the same proportions in all the red blood cells.

Table 3. Increased Proportions of Hb F in Adults

A. Persistence of Hb F synthesis beyond the neonatal period
   1. Congenital hemolytic anemias
      A. Sickle cell anemia
      B. Thalassemia
   2. Hereditary persistence of Hb F

B. Reactivation of Hb F synthesis
   1. Pregnancy
   2. Leukemia (Juvenile chronic myeloid leukemia)
   3. Aplastic anemia
   4. Miscellaneous

Weatherall has suggested that the amount of hemoglobin F found in sickle cell anemia and in thalassemia might simply represent the normal proportions of hemoglobin F made in the expanded marrow present in these diseases, together with selective destruction in the peripheral of non-F containing cells. This is an interesting hypothesis and some of the available data fit that hypothesis.

There are certain acquired disorders or conditions, such as normal pregnancy, in which fetal hemoglobin synthesis is reactivated. In 1955, it was first noted that pregnant women at midterm may have increased values for hemoglobin F. This has been observed since in several studies. The F isolated from the blood of pregnant women appears to be the adult type, suggesting that an agent diffuses across the placenta and transiently stimulates the production of fetal hemoglobin in the mother. Hemoglobin F in pregnant women appears to be heterogeneously distributed and its rise appears

to result from an increase in the number of F-containing cells.

Small increases in hemoglobin F are often observed in leukemias, but the only condition in which large amounts of hemoglobin F are regularly synthesized is in juvenile chronic myeloid leukemia. In this disorder, the red cells have fetal characteristics with respect to other markers such as hemoglobin A_2 and carbonic anhydrase. In aplastic anemia, an increased number of cells containing hemoglobin F has been observed in several studies.

The data concerning the hemoglobin F switch suggest that the changes in bone marrow and throughout the developing infant are coordinated under complex genetic control systems. The switch from beta to gamma chain or from gamma to beta chain may occur in distinct clones of adult red cell precursors. A possible exception may be in juvenile myeloid leukemia in which fetal clones of marrow cells may be activated.

At term there is a dramatic change in the overall level of erythropoiesis and red cell production is markedly reduced. After that time, beta synthesis is fully activated. This is, of course, reminiscent of the switch to gamma chain synthesis observed during recovery from aplastic anemia. Thus, both the chromosomal and cellular control of non-alpha chain synthesis remain to be clearly defined. An increase in or maintenance of hemoglobin F synthesis remains a goal in the treatment of sickling, but much remains to be learned about the mechanisms of the switch from gamma to beta chain synthesis, and about fetal and adult red cells, before we can even visualize manipulation of fetal hemoglobin synthesis.

RESULTS OF A DOUBLE-BLIND CLINICAL TRIAL OF ORAL SODIUM CYANATE IN PATIENTS WITH SICKLE CELL ANEMIA

Donald R. Harkness, M.D.

In April 1973, we instituted a two-year, double-blind, crossover study on the treatment of patients with sickle cell anemia with oral sodium cyanate. The following is a brief description of the design of this study and a report on the hematologic, therapeutic, and adverse effects of this treatment observed in 19 patients who completed the first 12 months on the study.

Study Design

Twenty-two patients (19 with homozygous sickle cell anemia and 3 with $S\beta^{o}$ -thalassemia), ranging in age from 18 to 49, were randomized into two groups. Twenty patients were selected because they had required treatment for painful crises in the emergency room at least three times or had been hospitalized for treatment once in the 6 months preceding entry into the study. One patient was entered because of the almost daily occurrence of priapism for 1 year and another because of the presence of large bilateral ankle ulcers for 5 years. One group of patients received NaNCO, 30 mg/kg/day, and the other group was given placebo (mannitol) in a similar dose. Patients were instructed to take the capsules orally with water in a single dose at bedtime. At the end of 6 months, the patients were switched from cyanate to placebo or vice versa.

Patients were seen in the clinic biweekly by physicians who were unaware of the type of medication being taken. Patients were queried about a group of randomized symptoms related to their disease and possible adverse effects of the treatment. A brief physical examination was performed which included assessment of muscle strength, deep tendon reflexes, and vibratory sensation in the extremities. On each clinic visit the following laboratory studies were performed: complete blood count, whole blood P_{50}, red cell 2,3-DPG, red cell G6PD activity, quantitative hemoglobin F, and valine hydantoin to assess the level of hemoglobin carbamylation. Biochemical profiles, T_3 and T_4, fractionated bilirubin, electrolytes, serum iron and TIBC, serum haptoglobin, prothrombin time, and partial thromboplastin time were measured at less frequent intervals. Chromium red cell survival and red cell mass were measured during each treatment period on most patients. A complete eye examination including slit lamp examination of the lens, direct retinal examination, fluorescein angiography, and electroretinography was given prior to the study and during each treatment period. Beginning in December 1973, a four-extremity sensory and motor nerve conduction velocity study and electroencephalogram were performed on all patients at 3- to 4-month intervals.

Significant painful crises were defined as moderate to severe pains occurring in two or more anatomic locations lasting 4 or more hours. If unrelieved at home in this period of time by oral medication (acetaminophen, propoxyphene, penazocine, oxycodone hydrochloride, or codeine), patients were instructed to come to the emergency room (grade III crisis); if hospitalization was required, the crises were designated as grade IV. Crises were subclassified as idiopathic and secondary on the basis of whether or not bacterial infection, deemed significant enough to require antibiotic therapy, was present. Crises were treated with intravenous hypotonic fluids, nasal oxygen, and intramuscular narcotics, usually meperidine along with promethazine hydrochloride. The study medication was continued during hospitalization. All patients with class IV crises and nearly all patients with class III crises were evaluated by one of the participating physicians.

Midway through each study period, questionnaires were completed by the patients with the aid of a social worker to evaluate their subjective response to therapy. To simplify the reporting of the data presented in this paper, in most instances the mean value for a given test determined during the placebo period is compared to its mean value while the patient was taking cyanate. To summarize the data for all patients, the values for all patients calculated as percent change from placebo to cyanate periods have been averaged.

The NaNCO used in these studies was kindly supplied by Dr. Anthony Cerami of Rockefeller University. Prior to use it was dissolved in distilled water (600 g in 6 L), treated twice

with Norit A (15 g), and recrystallized from 66 percent ethanol. After thorough drying, gelatin capsules were hand-filled with 300 ± 10 mg NaNCO and dispensed in quantities sufficient for a 2-week period.

The degree of hemoglobin carbamylation is reported as moles NCO^-/mole Hb which is measured as moles valine hydantoin/mole hemoglobin tetramer after acid hydrolysis of the hemoglobin. Under in vivo conditions, cyanate carbamylates hemoglobin almost exclusively at the α amino groups of the N-terminal valines of both α and β chains. The maximum theoretical carbamylation is therefore 4.0.

Results

Of the 22 patients entered into the study, one withdrew during the initial month of study, one was dropped due to noncompliance, and the clinical course was so complicated and confused on a third patient that her records were deemed not valuable. Among the remaining 19 patients, there was considerable variation in the average level of hemoglobin carbamylation. The mean carbamylation for the entire group of patients was 0.48 moles NCO^-/mole Hb with a range of 0.15 to 0.84. Four failed to achieve an average carbamylation of greater than 0.3 moles NCO^-/mole Hb. Undoubtedly some patients were not taking the prescribed number of capsules each day, despite constant urging to do so. A few patients complained of nausea and several took their medication with food or liquids other than water. It has previously been demonstrated that factors such as gastric pH and the presence of food in the stomach affect the amount of cyanate absorbed.

The mean decrease in P_{50} correlated well with the mean carbamylation achieved for the 19 patients (see Figure 47). Such a plot for any single patient more closely approximates a straight line. The average decrease in P_{50} per mole valine hydantoin was 6 torr, which agrees closely with values observed by others. Seventeen patients had a rise in hemoglobin while on cyanate. The correlation between mean carbamylation and change in hemoglobin concentration is not as close as that between carbamylation and increase in whole blood oxygen affinity (see Figure 48). These data indicate that one can expect an average increase in hemoglobin of approximately 1.6 g percent carbamylation of 1.0 mole NCO^-/mole Hb.

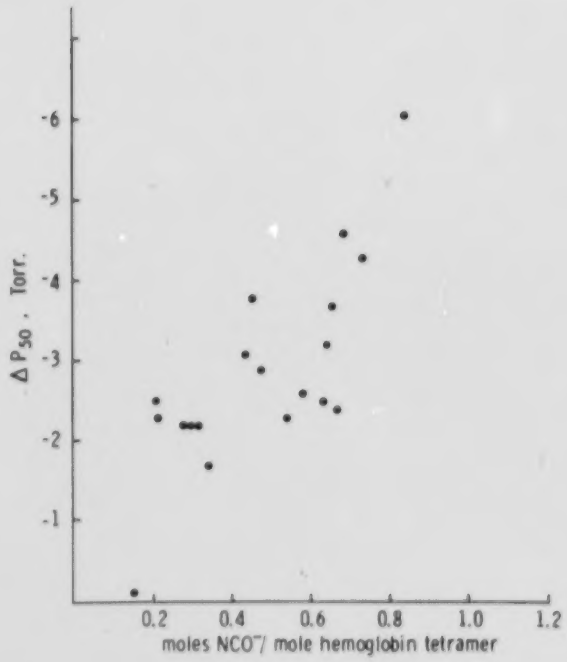


Figure 47. Relationship between mean carbamylation and mean increase in whole blood oxygen affinity in 19 patients.

There was an average increase in red cell mass of approximately 8 percent in the 16 patients on whom this measurement was made. In the 10 patients whose red cell mass increased, the mean carbamylation at the time of the measurement was 0.48 moles NCO^-/mole Hb (range, 0.1 to 1.0), whereas it was 0.43 moles NCO^-/mole Hb (range, 0.2 to 0.6) for the 6 patients with no increase in red cell mass. An increase in mean red cell survival occurred in 11 of these 16 patients. There is considerable scatter when this increase in survival is plotted against mean carbamylation (see Figure 49). The mean carbamylation at the time of measurement of red cell survival in the 11 patients who had the increased survival was 0.40 moles NCO^-/mole Hb (range, 0.1 to 1.0). Mean carbamylation at the time of the study in the 5 patients in whom an increased red cell survival was not demonstrated was 0.47 moles NCO^-/mole Hb (range, 0.2 to 0.9).

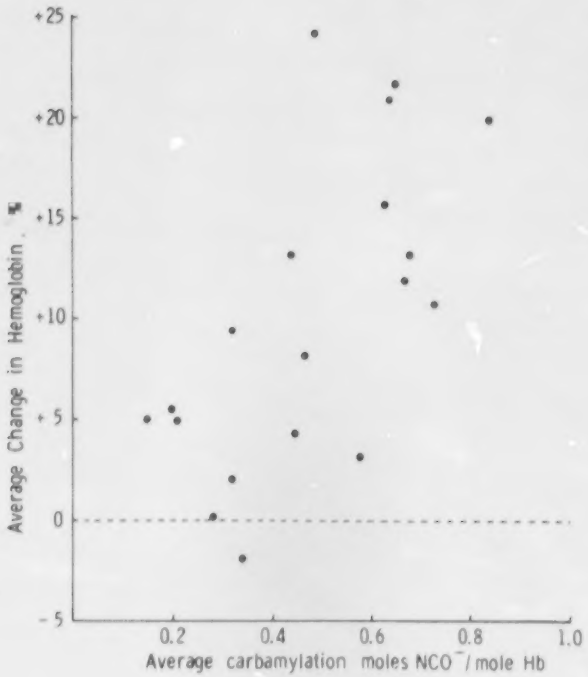


Figure 48. Relationship between mean carbamylation and mean percent change in hemoglobin concentration.

A summary of the hematologic parameters that changed during cyanate therapy is given in Table 4. Besides those mentioned above, there were moderate decreases in red blood cell 2,3-diphosphoglycerate (2,3-DPG) and total serum bilirubin levels and an average decrease in reticulocyte count of nearly 20 percent.

The mean red blood cell G6PD activity was 3.12 μmoles/ml rbc/minute in the 19 patients while they were taking the placebo; it fell to 2.93 μmoles/ml rbc/min while on cyanate. Based upon the relationship of G6PD activity to reticulocyte count during the placebo period, a decrease in reticulocyte count of 19 percent would be expected to decrease the G6PD activity to 0.23, giving an expected value of 2.89 μmoles/ml rbc/min during cyanate therapy. Therefore, the observed decrease is entirely consistent with what would be expected on the basis of the decrease in reticulocyte count, and there is no evidence of inhibition of G6PD activity by NaNCO in the erythrocytes of the patients while taking cyanate.

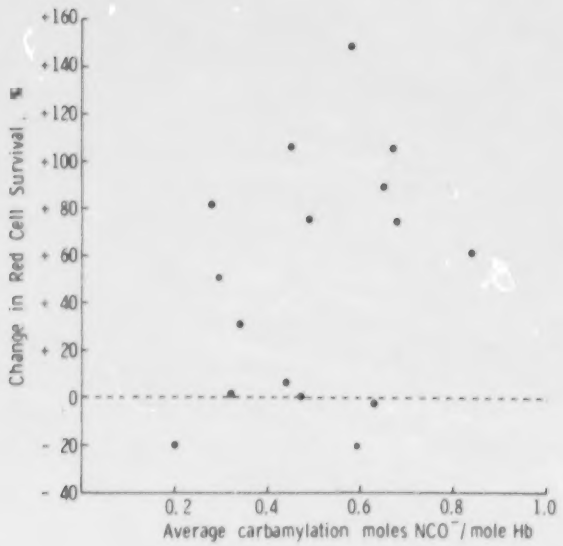


Figure 49. Effect of mean carbamylation upon red cell survival. The percent change in red cell survival was determined from single determinations of the chromium-tagged half-life while on placebo and while taking cyanate.

No changes were noted in lactic dehydrogenase, alkaline phosphatase, serum glutamic oxaloacetate transaminase, serum iron, prothrombin time, partial thromboplastin time, platelet count, white blood count, haptoglobin, electrolytes, blood urea nitrogen, calcium, phosphorus, serum proteins, T_3 and T_4, and hemoglobin F.

Despite the gratifying improvement in the hematologic parameters while the patients were taking cyanate described above, no decrease in the number of painful crises (class III and class IV) was noted. In Table 5 the total experience of 19 patients is summarized. There were 40 class III and class IV episodes of painful crises while the patients were on cyanate and 33 while they were taking the placebo. If the four patients who did not achieve a mean carbamylation above 0.3 moles NCO^-/mole Hb are excluded, as well as any crises that occurred between 0.1 and 0.3 moles NCO^-/mole Hb while the remaining patients were either starting or stopping cyanate, the results are the same (see Table 6). Looking at individual patients, 7 had more crises while on cyanate, 7 had more crises while on placebo, and 5 were unchanged

(two of these patients had no crises during the entire 12-month period of study). This distribution in response was totally unrelated to the level of carbamylation and therefore is probably random.

Four patients developed evidence of peripheral nerve damage while taking cyanate (see Table 8). In no case was the patient symptomatic. Nerve conduction velocity studies were not begun until December 1973. The first

Table 4. Mean Percent Change in Pertinent Hematologic Data in 19 Patients Taking Oral Sodium Cyanate for Six Months[a]

	Mean	Std.Dev.	SEM	n	Range
Carbamylation, moles NCO^-/mole Hb	0.48	0.20	0.05	19	0.15 to 0.84
P_{50}, torr	-9.28	3.86	0.88	19	-18 to 0
2, 3-DPG, μmoles/ml rbc	-5.22	6.60	1.51	19	-14 to 8
Hemoglobin, g %	10.13	7.76	1.78	19	-2 to +24
Packed cell volume, %	8.71	7.16	1.64	19	-2 to +19
Reticulocytes, %	-19.16	21.45	4.92	19	-54 to +21
Total bilirubin, mg%	-12.00	27.00	6.19	19	-50 to +60
Red cell mass, ml	7.94	13.29	3.32	16	-20 to +31
Red cell survival (T/2), da.	46.94	46.84	11.71	16	-20 to +150

[a]Values, excluding those for carbamylation, were derived by first calculating the mean values for each patient during placebo and cyanate treatment periods and calculating the percent change. The percent change for all patients was then calculated by finding the mean of these numbers.

Despite the failure to demonstrate symptomatic relief, responses to questionnaires from the 15 patients with carbamylation over 0.3 moles NCO^-/mole Hb indicated that they nearly all felt better while on the study. However, it did not seem to matter whether they were taking cyanate or the placebo, as shown in Table 7.

While taking cyanate, 7 of the 19 patients lost weight; 5 lost between 5 and 10 percent body weight, and 2 lost slightly more than 10 percent of body weight. None of 4 patients with carbamylation under 0.3 moles NCO^-/mole Hb lost weight. The two patients who lost the greatest amount of weight had mean carbamylations of 0.73 and 0.65 moles NCO^-/mole Hb.

patient with abnormalities was found in January 1974, 2 weeks after she had completed her first 6 months on sodium cyanate at a dose of 31.6 mg/kg/day. At the end of 6 months on placebo, her nerve conduction studies had not yet returned to normal. She was begun again on cyanate at 25 mg/kg/day and again had some increase in conduction abnormalities. Eight months after completion of her second 6 months on cyanate, her nerve conduction studies had returned to normal.

The second patient had taken cyanate in a dose of 22.1 mg/kg/day for only 14 weeks when nerve conduction abnormalities were noted. Despite continuation of therapy, nerve conduction

Table 5. Incidence of Crises in 19 Patients Completing One Year on Study[a]

	Placebo	Cyanate
Class III	22 (2)	23 (2)
Class IV	11 (2)	17 (6)
Total	33 (4)	40 (8)

[a]Class III: emergency room visit: Class IV: hospitalization, numbers in parentheses represent crises with concomitant infection.

Table 6. Incidence of Crises in 15 Patients Who Achieved a Mean Carbamylation Above 0.3 Moles NCO^-/Mole Hemoglobin[a]

	0.1 moles NCO^-	0.3 moles NCO^-
Class III	16 (2)	18 (2)
Class IV	7 (1)	11 (4)
Total	23 (3)	29 (6)

[a]Crises occurring between 0.1 and 0.3 moles NCO^-/mole Hb excluded.

was normal 4 months later and remained normal during a second treatment period with the same daily intake of cyanate. The third patient was shown to have abnormal nerve conduction studies 12 weeks after starting sodium cyanate on a dose of 26.4 mg/kg/day. Her patellar reflexes were decreased and Achilles' tendon reflexes were absent. The dose of cyanate was decreased to 20 mg/kg/day. At the time of completion of the cyanate treatment period, the nerve conduction studies were normal. Two weeks after crossing over to placebo, the patellar reflexes were normal and the Achilles' reflexes had returned to normal.

Table 7. Patient's Evaluation of Treatment[a]

	Total	Placebo	Cyanate
Improved	47	24	23
Unchanged	10	7	3
Worse	2	2	0

[a]Data tabulated only from the 15 patients whose average carbamylation while taking cyanate was over 0.3 moles NCO^-/mole hemoglobin.

The fourth patient with nerve conduction abnormalities had been taking cyanate for 20 weeks at a dose of 22.9 mg/kg/day when nerve conduction abnormalities were noted. Eleven weeks later (4 weeks after switching to placebo), nerve conduction studies were normal. Three of these four patients had high hemoglobin carbamylation; two patients experienced considerable weight loss. Had cyanate been discontinued when carbamylation levels rose above 0.8 mole NCO^-/mole Hb or with weight loss in excess of 5 percent body weight, this manifestation of cyanate toxicity might conceivably have been avoided.

One patient, a 24-year-old university student with $S\beta^o$-thalassemia and normal erythrocyte G6PD activity, began noticing glare and diminished visual acuity in bright light in September 1974, four months after beginning his second course of sodium cyanate. Ophthalmologic examination revealed visual acuity in the right eye of 20/16 and 20/30 in the left and the presence of bilateral amoeboid transparent posterior subcapsular cataracts.

Careful slit lamp examination of the lens, conducted before the patient had been entered into the study, had been normal except for scattered anterior and posterior cortical fleck-like opacities in each eye and vision was 20/20 in both eyes. After taking cyanate 30 mg/kg/day for 6 months, a second careful examination of the lenses revealed tiny axial posterior subcapsular cataracts bilaterally. Because of their minute size, it was believed they might have been missed on the initial examination.

Table 8. Patients Developing Nerve Conduction Abnormalities

Patient No.	Dose of NaNCO	Period of Treatment[a]	Total Dose	Maximum Carbamylation[b]	Average Carbamylation[c]	Weight Loss
	(mg/kg)	(weeks)	(g)	(moles NCO^-/ mole Hb)	(moles NCO^-/ mole Hb)	% (body wt.)
1	31.6	24	302	0.94	0.67	7
2	22.1	14	143	1.18	0.99	2.5
3	26.4	12	97	1.08	0.65	3.5
4	22.9	20	210	0.64	0.58	8

[a] Weeks receiving NaNCO at time nerve conduction abnormalities were first observed.

[b] Maximum carbamylation during 12 weeks preceding observance of nerve conduction abnormalities.

[c] Average carbamylation during 12 weeks immediately preceding observance of nerve conduction prolongation.

At the end of the placebo period, the same careful observer did not describe the presence of these small cataracts. The patient was again begun on oral cyanate, 25 mg/kg/day, and the visual symptoms and discovery of the large cataracts occurred four months later. The drug was immediately discontinued. In December, upon repeat examination, the cataracts had completely disappeared, the patient described no visual symptoms, and visual acuity had returned to normal. Subsequent follow-up examinations have been normal.

Other investigators using oral cyanate in patients had been informed of the occurrence of cataracts in our patient shortly after we discovered them. A second patient with cataracts was found among the patients being treated at Rockefeller University in December 1974. This patient had started oral sodium cyanate in a dose of 35 mg/kg/day taken in three divided doses with meals in October 1971. Because of weight loss, the dose was decreased to 20-25 mg/kg/day in May 1973. His red blood cells had the African type (A^-) G6PD deficiency. We had the opportunity to examine this patient at the Bascom Palmer Eye Institute at the University of Miami in February 1975. The cataracts were located in the same region of the lens as in the first case but had a more dense, ground glass appearance. Follow-up examination in June 1975 failed to detect any change in the appearance of these cataracts.

A complete description of these two patients has been reported in the literature * and we have discussed the pathogenesis of cyanate-induced cataracts in a recent review.** Very recently, the presence of similar cataracts in dogs treated with carbamyl phosphate and in dogs treated with sodium cyanate has been observed.

Comments

The data from the first 12 months of this study clearly indicate that most patients placed on oral sodium cyanate show improvement in red cell mass, red cell survival, hemoglobin and packed cell volume. Those showing no improvement were primarily those in whom carbamylation of hemoglobin was low, presumably due either to failure to take the prescribed number of capsules or to failure to absorb the medication. These results are in agreement with previous reports.

In contrast to the encouraging hematologic response, the data reported in this paper do not indicate symptomatic improvement in the patients while taking cyanate. Although the patients were nearly unanimous in describing subjective improvement while they were participating in the study, the same response was given when they were taking the placebo as when taking cyanate. A review of the data on those patients who have completed the second year on this study, and an additional 8 patients treated in Jacksonville for 12 months following this same protocol, reveals no significant departure from the preliminary results reported above and summarized in Table 9. The failure to demonstrate a decrease in painful crises in this double-blind crossover study is discouraging; these results clearly differ from those obtained in retrospective fashion in the first clinical assessment of this drug carried out at Rockefeller University.

The failure to decrease the number of painful crises with cyanate therapy in the presence of an increase of red cell mass seems contradictory but may be explained, at least partially, by an increase in viscosity of blood as the hematocrit rises. In a recent study, androgen therapy in patients with sickle cell anemia had to be discontinued after three patients developed increasing symptomatology as the hemoglobin rose. It may be that patients who undergo treatment by extracorporeal carbamylation would benefit by controlled phlebotomy to maintain the hematocrit at pretreatment levels.

The reported clinical toxicities of cyanate in man include weight loss, reversible peripheral neuropathy, and development of cataracts. All were seen in patients in this study. These have been adequately described elsewhere and will not be discussed here. It was the discovery of the cataracts that finally lead us to terminate this study, which we did in February 1975, after examining the second patient from Rockefeller University.

In seems clear that the toxicities already described, and the potential for other toxic manifestations not yet uncovered, preclude further studies on orally administered sodium cyanate in man. Many other anti-sickling agents now being studied possess equal or greater potential for harm to the patient. It is for this reason that the current interest in methods for the extracorporeal treatment of blood is timely, since this approach to therapy,

Table 9. Incidence of Crises in 22 Patients Who Achieved a Mean Carbamylation Above 0.3 Moles NCO^-/Mole Hemoglobin* (Miami and Jacksonville).

	<0.1 moles NCO^-	>0.3 moles NCO^-
Class III		
Miami - year 1	15	18
year 2	5	2
Jacksonville	1	0
Class IV		
Miami - year 1	8	10
year 2	3	1
Jacksonville	0	0
Total	32	31

*Crises occurring between 0.1 and 0.3 moles NCO^-/hemoglobin tetramer excluded.

when employing such highly reactive chemicals, should theoretically minimize the risks to the patient.

Summary

1. The results of the first 12 months of a double-blind crossover assessment of the efficacy of oral sodium cyanate therapy (30 mg/kg/day in a single dose at bedtime) in 19 patients with sickle cell disease (16 homozygous for S and 3 doubly heterozygous for S and β°-thalassemia) are presented.

2. Marked variation was noted in the mean levels of hemoglobin carbamylation achieved in these patients: mean carbamylation for the group was 0.48 moles NCO^{-}/mole hemoglobin tetramer with a range of 0.15 to 0.84. Four patients had mean levels of carbamylation of less than 0.3.

3. There were mean increases in hemoglobin (10.1 percent), hematocrit (8.7 percent), red cell mass (7.9 percent), and red cell survival (46.9 percent) and mean decreases in reticulocyte count (-19.6 percent), total bilirubin (-12.0 percent), red cell 2,3-DPG (-5.2 percent), and P_{50} (-9.3 percent). For individual patients, these changes correlated roughly with the level of carbamylation.

4. No decrease in the total number of painful crises requiring treatment in the emergency room or hospitalization was noted while the patients were on cyanate. Seven patients had more crises and 7 had fewer crises while taking cyanate. These 14 patients were randomly divided between those with higher and lower levels of carbamylation.

5. Toxic manifestations of the oral cyanate observed included:
   a. weight loss - two patients lost more than 10 percent total body weight, and an additional five lost between 5 and 10 percent total body weight;
   b. neurotoxicity - four patients had evidence of peripheral nerve damage evidenced by prolongation of nerve conduction velocity, all had returned to normal within 8 months after discontinuance of cyanate therapy; and
   c. cataracts - one patient developed large bilateral posterior subcapsular cataracts which had completely disappeared 3 months after withdrawal from cyanate.

6. It is concluded from these studies that since significant toxicity is associated with the oral administration of sodium cyanate in doses of 30 mg/kg/day to man and since no therapeutic benefit could be demonstrated (i.e., decrease in painful crises) at this dosage level, further clinical trials of oral sodium cyanate should be discouraged.

Acknowledgments

This work was supported by USPHS Grant HL-15999 and the Veterans Administration.

*Nicholson, D.R., D.R. Harkness, W.E. Benson, and C.M. Peterson: Cyanate-induced cataracts in patients with sickle cell hemoglobinopathies. Arch. Ophthalmol. 94: 927-930, 1976.

**Harkness, D.R., and S. Roth: Clinical evaluation of cyanate in sickle cell anemia. In E. B. Brown, ed. Progress in Hematology, vol. 9, Grune and Stratton, New York, 1975, pp. 157-184.

EXPERIMENTAL APPROACHES TO THERAPY AND SICKLE CELL ANEMIA -- UREA AND ALKALI

Robert S. Rhodes, M.D.

Therapy of sickle cell disorders, particularly vascular occlusive crisis, remains an enigma. Numerous experimental approaches have surfaced and resurfaced over the past 20 years, ranging from hypotonic fluids, alkali, urea, cyanate, and carbon monoxide, to hyperbaric oxygen, and so on. All of these therapies have the common goal of unblocking occluded microvasculature by either unsickling or diluting sickled cells.

In spite of the wealth of knowledge available on the mechanism of sickling and the chemistry of hemoglobin S, little to nothing of real therapeutic effectiveness has surfaced. Much of the thinking surrounding the approaches reviewed in this presentation has been directed toward either an attempt to modify structural changes in sickle hemoglobin or toward altering the milieu of the sickled cells, which would somehow produce a desickling effect.

Alkali Therapy

In 1954 a report by Diggs and Bruegge mentioned the influence of acidosis on the sickling mechanism. Other reports over the next 10 years, including Haddad et al., 1956, and Kong and Alleyne, 1969, confirmed in some detail a relationship between sickling and acidosis. It was only natural that, following these reports, there was extensive experimentation and claims of great success using alkali to reverse the sickling process and to treat the vascular occlusive phenomenon. In 1955 Barreras reported great success in treating sickle crisis with alkali in the form of sodium bicarbonate, I.V. In 1964 Barreras, working in collaboration with Diggs, again reported what appeared to be a rationale, also noting some success using sodium bicarbonate to treat painful crises in a group of patients in Memphis. Other researchers, including Hugh-Jones, and Lehman and McAlister in 1964, extended the use of alkali to other agents including magnesium compounds.

After enjoying a long look by many clinicians and investigators using various approaches, alkali fell into disuse until the publication of a widely circulated report by Diggs and Barreras in the Journal of the American Medical Association in 1971, which reported success in treating nine patients in early sickle cell crisis using alkali in the form of sodium citrate in 10 percent solution orally. In the same study they also reported success in the use of M/6 lactate intravenously and stated the duration of crisis was significantly reduced in both groups of patients treated with alkali compared with another group of patients receiving codeine and nonalkaline intravenous fluids.

Further studies on alkali were conducted and reported on in 1974 by the cooperative urea trials group. Among other things, this group compared the use and effectiveness of alkali therapy with urea I.V. and hydrating fluids in a double blind clinical trials study. One of the groups in this study (Meharry and Vanderbilt in Nashville, Tennessee) reported that in comparing the efficacy of M/6 sodium lactate versus one-quarter normal saline solution in alleviating painful vaso-occlusive crisis, the results revealed no statistically significant differences between the two groups in the number of remissions within 48 hours of the onset of therapy. They reported some evidence that patients with low initial pH values seem to do better when treated with alkali than with simple hydration alone. During the two-year period of the study, a total of 43 crises were treated on the protocol. Twenty-three crises were treated with dextrose one-quarter normal saline solution and 20 with M/6 sodium lactate solution. Minimal side effects were reported associated with the study.

Another arm of the cooperative study group looked at bicarbonate as a mode of alkali therapy in a double blind control fashion. This protocol group consisted of Bowman Gray, Duke University, Emory University, and the University of Tennessee Schools of Medicine. They reported no significant response to alkali therapy during the 48-hour period when it was contrasted with nonalkaline hydrating solutions.

Urea Therapy

From 1967 to 1969 work was published by Murayama and others on structure and

structural changes in oxyhemoglobin and deoxyhemoglobin S involving hydrophobic bonding and its involvement in the sickling process. Other studies based on the role of hydrophobic bonding in the production of sickling led to recognition of urea's unique chemical properties which could affect sickling. These include:

- Small molecular dimensions
- Metabolically inert compound
- Generally nontoxic
- Water soluble
- Ability to disrupt hydrophobic bonds

As early as 1954, however, Ponder and Ponder had reported the effectiveness of aqueous urea solution in the inhibition and reversal of sickling in vitro. However, they also noted marked hemolysis when this agent was used. Other studies confirmed the use of urea in invert sugar in high concentration as an effective agent in the reversal of sickling, without accompanying hemolysis.

Using the previously demonstrated safety of urea in treating cerebral edema as a basis for their proposal, several investigators, including Nalbandian and others in 1970, and McCurdy et al., reported successful termination of vaso-occlusive crisis in uncontrolled nonblinded studies of urea and invert sugar.

Reports, both published and unpublished, mushroomed and controversy ensued concerning the effectiveness and safety of this agent. Many of the early reports emphasized the fact that urea therapy should be considered extremely tenuous at best as far as efficacy was concerned and that it was considered as strictly experimental.

As a result of widespread attention in the press and the controversy in the interested medical and lay world, the National Heart and Lung Institute undertook development of the cooperative controlled double blind study on the effectiveness of urea administered intravenously as a treatment for sickle cell vaso-occlusive crisis. The study was designed to determine if large doses of urea in invert sugar administered intravenously would abort painful sickle cell crisis, if the benefit and safety ratio were appropriate for widespread clinical use, and also, if the required precautions were practical, etc. Each study was designed with the idea that to be considered effective and have an adequate or at least a satisfactory therapeutic index, urea infusion should have broken the crisis within 24 hours of the start of treatment. This criterion was necessitated by the problems associated with the use of this agent over prolonged periods of time. The therapeutic index resulting from observations made during this study indicated that urea was not significantly effective in halting or shortening painful sickle cell crises. These observations were in marked contrast to the several anecdotal reports which maintained that unblinded, noncontrolled studies testing this agent continued to maintain a high success rate.

At this time most investigators have concluded that, while urea can in fact affect gelation of sickle hemoglobin, in vitro use minimizes the therapeutic index of effectiveness to the point where it is considered ineffective in contrast with less dangerous approaches including simple hydration and the use of analgesia.

While I am certain that most of us in the room are familiar with these studies, I simply report this information to remind us that the use of urea is a good indication that in the area of research in sickle cell crisis, there is much to be learned. We must also be aware of the fact that great harm stands to result from the use of agents without appropriate clinical investigation.

THEORETICAL APPROACHES TO THE TREATMENT OF SICKLE CELL DISEASES

Donald R. Harkness, M.D.

It is probable that at least six pairs of genes, one of each pair derived from each parent, make up the normal complement of DNA which codes for the four types of polypeptide chains contained in the hemoglobin tetramers of newborns and adults (Figure 50). These hemoglobins are composed of two α chains and two non-α chains: Hb A, $\alpha_2\beta_2$; Hb F, $\alpha_2\beta_2$; and Hb A_2, $\alpha_2\delta_2$. Tetramers consisting of four identical chains (Hb H, β_4; Bart's Hb, γ_4) do not function in oxygen transport.

established with certainty. However, there are at least two alleles (4 genes), and these are identical except at position 131 where the $^{A}\gamma$ gene codes for an alanine and the $^{G}\gamma$ gene codes for glycine. Gamma chain synthesis commences very early in fetal life and hence the major hemoglobin tetramer present in the fetus is Hb F.

There is but a single set of genes which codes for the δ chains present in the minor hemoglobin A_2. These genes have considerable

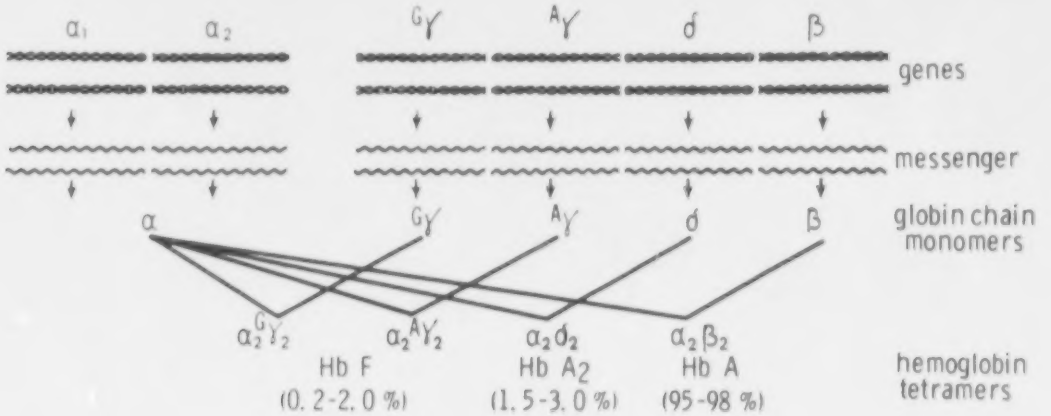


Figure 50. Normal Hemoglobin Formation. The quantities of hemoglobin tetramers indicated at the bottom of the figure are the normal values in the adult.

The α genes have been duplicated so that in most populations of man there are four identical genes. Synthesis of α chains begins early in the first trimester of pregnancy and continues throughout life. It has recently been demonstrated that, at least in Orientals, the four types of α thalassemia result from the deletion of one (α thal "silent"), two (α thal trait), three (hemoglobin H diseases), and four (hydrops fetalis) of these structural genes. Because there are four genes, heterozygous α chain structural mutations usually give rise to somewhat less than 25 percent of mutant Hb A and small quantities of mutant Hb F and Hb A_2.

The γ chains have also been duplicated but the exact number of genes has not been

homology with β genes. Although δ genes become activated shortly after birth, Hb A_2 normally does not exceed 2.5 percent of the total hemoglobin. It is elevated in most types of β thalassemia trait and in some types of homozygous β thalassemia; it may be depressed in iron deficiency.

There is only one pair of genes which codes for the β chains. Beta chain synthesis begins before the end of the first trimester of fetal life and increases gradually; at birth about 20-30 percent of the hemoglobin is Hb A. Gamma chain synthesis diminishes as β chain synthesis increases so that α and non-α chain synthesis is balanced. By the end of the first year of life Hb F levels are usually down to the 1 percent

levels seen in the adult and the hemoglobin "switchover" is completed.

Because there are only two β genes, the erythrocytes of persons heterozygous for β chain structural mutations contain 50 percent of less mutant hemoglobin. Persons who are heterozygous for β thalassemia may make no normal β messenger (β° thalassemia) or may synthesize decreased amounts of normal β messenger RNA on the thalassemic gene (β^+ thalassemia). In β° thalassemia the β gene is either deleted or present but "inactive."

Sickle cell hemoglobin (Hb S) has a structural mutation in the β6 position with valine replacing the normally occurring glutamic acid. Theoretically the erythrocytes of persons heterozygous for Hb S (S trait, A/S) should contain approximately 50 percent Hb S. In fact, there has been noted a trimodality in distribution of Hb S in these heterozygotes, with most having somewhat more than 40 percent Hb S, a smaller number having approximately 35 percent, and an even smaller number having an average of 28 percent Hb S.

Recently it has been demonstrated that persons in these three groups have different numbers of active α gene loci: four, three, and two, respectively. It has not yet been proved whether or not these inactive α genes represent deletions as in the α thalassemias found in the Orient. The preference for forming Hb A instead of Hb S in the presence of limited amounts of α chains appears to result from the formation of a more stable tetramer with normal β chains; also β^S chains are less stable than β chains. With rare exceptions persons with S trait live an entirely normal life, free of the complications seen in the sickle cell diseases.

Now let us consider the various types of sickle cell diseases. Persons who inherit the β^S gene from each parent have sickle cell anemia or S/S disease. Their red cells contain a normal concentration of hemoglobin which consists of variable but usually increased amounts of Hb F, normal amounts of Hb A_2, and predominantly, Hb S. Deoxyhemoglobin S is much less soluble than oxy-Hb S and deoxy-Hb A, and associates into linear aggregates which distort the erythrocyte into the brittle sickled forms. These sickled cells have a shortened survival -- hence the anemia. They are poorly deformable and may slow or stop flow of blood through portions of the microcirculation causing pain, tissue necrosis, and fibrosis. This property of the cells accounts for most of the symptomatology and pathology of sickle cell diseases.

The other forms of clinically significant sickle cell diseases occur in mixed heterozygotes who inherit the S gene from one parent and either a gene for one of several other β chain structural mutations (C, D, O_{arab}) or a form of β thalassemia from the other parent. Hemoglobins C, D, and O_{arab} coaggregate with S hemoglobin to variable extents, so sickling may occur within the circulation. The symptoms of persons with S/C and S/D hemoglobinopathies are clinically much milder than those with S/O_{arab} and S/S. In general, the clinical severity correlates inversely with the minimum gelling concentration of solutions of 1:1 mixtures of Hb S and the other hemoglobin. Mixtures of hemoglobin S and O_{arab} have a minimum gelling point very similar to that of Hb S alone.

In S/β^+ thalassemia the erythrocytes contain more than 50 percent Hb S (frequently 70 percent or 80 percent), a modest elevation in Hb A_2 and Hb F, and up to 40 percent Hb A. In general, the greater the proportion of Hb S, the greater the clinical severity. This disease is usually considerably milder than S/S disease. In S/β° thalassemia, since the only β gene that is expressed is the β^S gene, Hb A_2 and Hb F are elevated but all of the rest of the hemoglobin is S (Figure 51). Usually persons with S/β° thalassemia have a milder clinical course than do those with S/S disease. This is thought to result primarily from the lower concentration of hemoglobin within the erythrocyte, creating less tendency for the cells to sickle.

Finally, in this introduction we must consider the influence of Hb F upon sickling. Studies with mixtures of Hbs S and F reveal that Hb F has a significant inhibitory effect upon gelling. Many patients with S/S disease have elevated levels of Hb F and at one time it was considered that the higher the Hb F, the less severe the disease. Recently this belief has been questioned; it has been shown that the Hb F in these patients is heterogeneously distributed. Some cells have almost all Hb F and do not sickle, but most of the cells have low Hb F and readily sickle. There exists one condition called "high persistent fetal

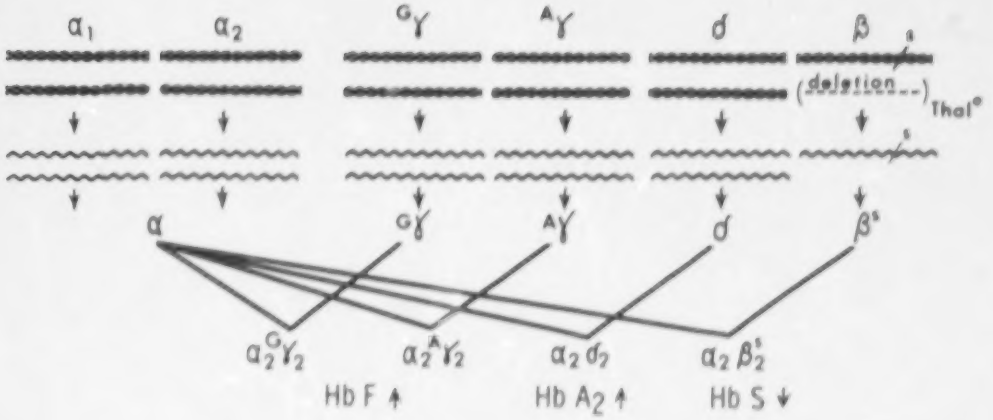


Figure 51. S/β° Thalassemia. In this representation the β° thalassemia gene is depicted as a deletion. Note that Hb F and Hb A_2 are increased, there is no Hb A, and the predominant Hb is S. The total Hb present in the erythrocytes is less than in cells of normals.

hemoglobin" (HPFH) in which there is a deletion of both β and δ genes and high levels of Hb F persist in every cell. In persons with S/HPFH, all cells contain about 70 percent Hb S and 30 percent Hb F. This is a very benign disease. One exception to the above story is the benign form of sickle cell disease described in Arabs who have approximately 20 percent Hb F distributed heterogeneously.

Before considering various theoretical approaches to therapy of sickle cell disease, let me summarize what we have learned from the above discussion. Hb S aggregates only when deoxygenated; certain hemoglobins co-aggregate with Hb S; Hb A within the cell "dilutes" the concentration of Hb S, making it less likely to aggregate; and Hb F has a definite inhibitory effect upon Hb S aggregation. Finally we have learned that the lower the concentration of Hb S within the cell (such as in S/β° thal), the less tendency there is for sickling.

Now let us consider some of the approaches to therapy. I shall briefly discuss those listed in Table 10. The first item deals not with treatment but with prevention. Although the legislators who passed the original Sickle Cell Act in 1972 perhaps thought otherwise, it seems very clear to most of us that the incidence of births of infants with sickle cell disease will not be significantly decreased by programs of public education and screening. Although prenatal diagnosis has been accomplished with acceptable accuracy, this is currently an expensive, time-consuming procedure with risk to the fetus and it is only available in a few centers around the world.

Table 10. Theoretical Approaches to Treatment of Sickle Cell Anemia

1. Prevention through education, prenatal diagnosis
2. Suppression of hemoglobin switching
3. Bone marrow transplantation
4. Decreasing cellular hemoglobin concentration
5. Chemical approaches
   a. heme-directed
   b. increase in oxygen affinity
   c. direct interference with aggregation
   d. membrane-directed
   e. other
6. Other - ?

Many laboratories are examining possible means of preventing the switchover from Hb F

to adult hemoglobin. If it were possible to do so, not only would this be a means of treatment for the sickle cell diseases but also for other hemoglobinopathies affecting the β chain. Since the diagnosis of sickle cell diseases can be made readily at birth, therapy could be instituted immediately. Others are working on ways to switch back to Hb F synthesis. If successful, this could provide a means of treatment after hemoglobin switchover already has occurred. Although this approach is exciting and has great theoretical potential, significant manipulation of hemoglobin switching has yet to be achieved in the laboratory.

Advances in the technology of bone marrow transplantation in the recent past have been quite remarkable. Bone marrow transplantation using an identical twin as donor is highly successful and involves little risk to the recipient but is, of course, of no use in treatment of hereditary diseases. Transplantation from a non-identical twin or from other HLA-matched donors requires lethal irradiation of the recipient and prolonged immunosuppressive therapy. If the transplant is not successful, the patient expires from the irradiation; if the marrow does take, problems with graft-versus-host reactions occur in many recipients. Therefore, at least at the present time, no one is willing to advocate this form of therapy in persons with nonlethal diseases.

Lowering the concentration of hemoglobin within the erythrocyte of patients with S/S disease might reduce the ease with which the cells sickle and thereby diminish the severity of the disease, as in S/β^0 thalassemia. One well-established mechanism for producing hypochromia is by creating iron deficiency; this approach (by periodic phlebotomy) currently is under study. Other approaches might be feasible such as induction of unbalanced globin chain synthesis (that is, by lowering α chain synthesis), creating not only hypochromia but possibly favoring combination of the limited α chains with γ and δ chains (or β chains in S/β^+ thalassemia).

Let us now turn to consideration of the use of various chemicals that influence sickling. We know that simple dilution of the Hb S within the cell with nonsickling hemoglobin lowers the likelihood of intravascular sickling (e.g., A/S or S/β^+ thal). We also know that Hb S aggregates only in the deoxy conformation. Both methemoglobin and carboxyhemoglobin are "fixed" in the oxy conformation. Beutler tried giving patients with S/S disease small amounts of oral sodium nitrite with the aim of converting about 15 percent to 20 percent of the hemoglobin to methemoglobin. This approach was abandoned primarily because it proved difficult to safely predict individual response and to maintain relatively constant proportions of methemoglobin.

Perhaps this approach justifies further study. It must be recognized, of course, that methemoglobin does not function in oxygen transport so that initially, prior to an erythropoietin-mediated increase in red cell mass, the patient is actually made more "anemic." In addition, any benefit derived by decreased tendency for sickling might be offset by the rising blood viscosity that would occur as the hematocrit increased.

Sirs, using similar reasoning, tried without convincing success to treat a painful crisis in a patient by having him breathe carbon monoxide. This form of therapy, which would seem to have potential therapeutic benefit only during crisis (most other therapy under discussion is aimed at prevention of crises), is currently under further investigation. It seems to me that such therapy is dangerous. Its use is obviously impractical in terms of chronic therapy, and it is unlikely that during crises carboxy-Hb S loaded cells would get into the areas where blood flow had slowed or stopped due to sickling. This last point holds true for almost anything we do in terms of therapy during the crisis.

Another approach to therapy of sickle cell diseases is to induce a left shift in the oxygen dissociation curve (decrease the P_{50}; increase the affinity of the hemoglobin for O_2). This approach is depicted in Figure 52. The oxygen dissociation curve is shifted to the right in S/S disease due to increased intracellular concentrations of 2,3-diphosphoglyceric acid (2,3-DPG) and probably the energy involved in hemoglobin polymerization is also a contributing factor. In any other form of anemia this right shift would be beneficial since the amount of oxygen which dissociates from the hemoglobin at any given pO_2 is increased. However, in sickling disorders, once a certain percentage of the hemoglobin (depicted as 70 percent in Figure 52) is in the deoxy form, the cell sickles.

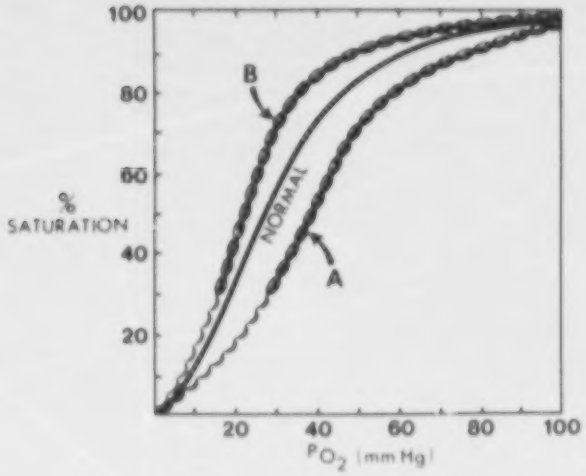


Figure 52. The Effects Upon Sickling of Shifting the Oxyhemoglobin Dissociation Curve to the Left. Curve A depicts the whole blood oxyhemoglobin dissociation curve in sickle cell anemia. Note that sickling only occurs when about 70 percent of the hemoglobin is deoxygenated. In curve B, the curve is drawn to the left of normal making the cells much less likely to sickle at any given pO_2.

Therefore this right shifted curve actually exposes the cells to a greater risk of sickling. Any left shift in the curve would decrease the likelihood of sickling, assuming (as is the case) that capillary pO_2 does not decrease significantly.

There are a number of ways to decrease the P_{50}. The most obvious method is to increase intracellular pH, which is most readily accomplished by inducing systemic alkalosis. Administration of alkali to patients during painful crises has been a common practice for years. Without going into this at length, I will simply say that a number of studies indicate that the administration of bicarbonate or lactate does not shorten the crisis. Most persons now employ alkali during painful crises only if the patient is acidotic. It is very difficult to raise blood pH chronically as a means of preventing crises. Even if it were possible, increased intracellular pH serves as a potent stimulus to 2,3-DPG synthesis which accumulates and shifts the oxygen dissociation curve back to the right.

Another way to lower the P_{50} is by lowering the concentration of 2,3-DPG within the erythrocyte. Acidosis does this quite effectively but itself shifts the oxygen dissociation curve to the right. Diets low in inorganic phosphate lower serum phosphate and cause lowering of 2,3-DPG. However, after about three months on a low phosphate diet patients develop bone pain. Furthermore, hemolytic anemia develops in persons with very low serum phosphate secondary to diminished erythrocyte glycolysis. Various known activators of 2,3-DPG phosphatase are either too toxic to use clinically or do not cross the erythrocyte membrane. Glycolic acid does cross the membrane and can be phosphorylated by the enzyme pyruvate kinase forming phosphoglycolate, which is a very potent activator of the phosphatase.

In in vitro studies we were unable to induce red cell depletion of 2,3-DPG except with very high concentrations of glycolate. In rabbits we observed no decrease in 2,3-DPG after chronic administration of very large amounts of sodium glycolate. To summarize, there is presently no way to lower red cell 2,3-DPG safely and chronically.

The most promising way to shift the oxygen dissociation curve to the left is with the chemical cyanate. This compound reacts irreversibly with the α-amino groups of both the α and β chains of hemoglobin. Carbamylation at these sites lowers the P_{50} and inhibits sickling. Much work has been done with cyanate as I noted earlier. I will only mention here that the oral dose required to significantly lower the P_{50} is high enough to induce unacceptable clinical toxicity and further studies on its oral use have been abandoned. Presumably the toxicity results from carbamylation of proteins other than hemoglobin. This problem can be circumvented by drawing blood from patients, reacting it with cyanate, and then removing the unreacted drug before returning the blood to the patient. Clinical trials with cyanate used in this way are currently being conducted by Diederich and preliminary reports appear promising.

Another group of compounds which is being studied is cross-linking bifunctional reagents, such as dimethyl adipimidate, methyl acetimidate and dimethyl-3,3'-dithiobispropionimidate. At least some of these lower the P_{50} but they also create stable bonds between hemoglobin tetramers. The "anti-sickling" properties of these chemicals do not result entirely from their effect upon oxygen affinity since effects on solubility can be measured in the absence of oxygen. These

compounds are highly reactive, and it seems unlikely that any of them will come to clinical trial unless perhaps by the extracorporeal approach.

Let us now consider chemicals which decrease sickling, not by effecting changes in oxygen affinity, but by retarding or diminishing the protein-protein interaction involved in aggregation of Hb S, thereby increasing its solubility. These compounds could act by modification of the perturbation of the N-terminal portion of the β^S chain induced by the insertion of valine in the β6 position, by altering the complementary sites which must be involved in the aggregation of HB S or by a combination of the two.

Urea was the first of this group to be studied. Whereas it is true that very high concentrations of urea do increase hemoglobin oxygen affinity, at the concentrations necessary to alter the solubility of Hb S there is little change in P_{50}. The other group of compounds which have potent anti-sickling properties thought to be independent of changes in oxygen affinity are the nitrogen mustard alkylating agents. At least some of these have been shown to react specifically with the histidine at β2. Since these highly reactive compounds have well-known suppressive effects upon bone marrow and other rapidly proliferating tissues, they could probably be used only extracorporeally in clinical trials.

Before discussing the presumed mechanism of action of the compounds I will group under "membrane-directed," let us digress just a moment and discuss the erythrocyte membrane in sickle cell disease. Two types of sickled cells are present in the blood of persons with S/S disease: (1) reversibly sickled cells (RSC) which upon oxygenation revert to normal morphology and (2) irreversibly sickled cells (ISC) which remain permanently sickled even after equilibration with 100 percent O_2. RSC can be converted to ISC by repeated sickling and unsickling or by prolonged anaerobic incubation.

Although fully oxygenated ISC remain deformed, on electron microscopy the hemoglobin is not polymerized, suggesting irreversible changes in the membrane. Further evidence that some alteration in the membrane has occurred is inferred both from the increased permeability to cations of these cells and reported alterations in electrophoretic mobilities of some of the membrane proteins. It has recently been shown that sickle cells contain more calcium than normal cells (about 3-fold) and that ISC contain several-fold more than RSC. It has been known for quite some time that even normal cells become rigid when calcium-loaded. It is suspected that ISC formation is related to membrane alteration with secondary calcium loading.

Procaine hydrochloride has been reported to increase the filterability (deformability) of erythrocytes from persons with S/S disease. I do not think the mechanism of this effect has been proven, but it is suspected that procaine may have an effect upon calcium transport. Dr. John Harris, in a recent conversation we had, indicated that many years ago he gave procaine intravenously to patients in crisis and that it had no effect whatsoever on the patient's pain!

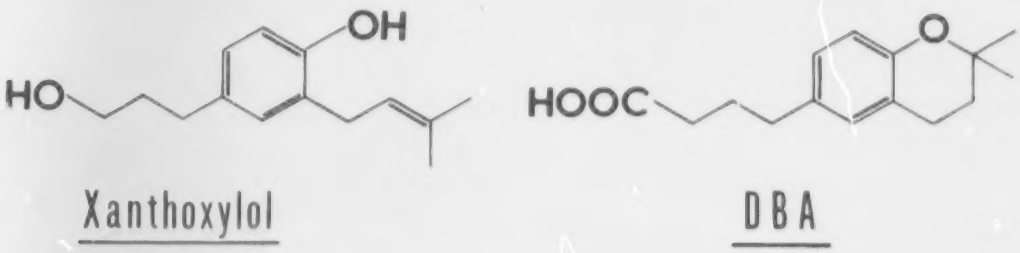
Currently there is considerable interest in zinc as a possible treatment for S/S disease. Many persons with S/S disease have low serum and red cell zinc levels and excrete excessive zinc in the urine. Dr. Ananda Persad, who originally described zinc deficiency in young males with hypogonadism and dwarfism in the Middle East, has reported that several adolescent hypogonadal boys with S/S disease matured after oral zinc therapy. Dr. Graham Serjeant reported that leg ulcers in sickle patients with low blood zinc levels healed more promptly when oral zinc was given.

Brewer, Prasad and their associates have demonstrated that patients treated with oral zinc have a decrease in ISC in the circulation. They also found that S/S erythrocytes incubated with Zn^{++} and then infused into rats circulate longer than control S/S erythrocytes. These investigators have reported preliminary data suggesting that patients have fewer crises while taking zinc. They are now conducting a double-blind clinical study to verify their belief that zinc therapy will prove useful in treating persons with S/S disease. The mechanism by which zinc acts is thought to be prevention of calcium loading by competition for the same membrane transport system.

Finally this talk would not be complete without mentioning the studies on extracts of African chewing sticks made from the root of Fagara

xanthoxyloides. It has been reported that xanthoxylol (see Figure 53) is the chemical responsible for the anti-sickling properties of these extracts. A compound similar to this, 3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-6-butyric acid (DBA), has been synthesized and is reported to have potent anti-sickling properties and little toxicity in animal studies. Its mechanism of effect on sickling is unknown. At least for the moment DBA can be placed in Table 10 under 5e!

In conclusion let me reiterate that much is now known about the sickling process and the cellular factors which influence it. In the last few years we have witnessed a tremendous expansion of research efforts to discover a safe and effective treatment for sickle cell anemia. Hopefully, with the leads now available, and perhaps even with some of the compounds described above, within the next few years we will have efficacious therapy for persons with these diseases.



Xanthoxylol DBA

Figure 53. Xanthoxylol is the presumed anti-sickling chemical isolated from the African chewing sticks, the root of Fagara xanthoxyloides. DBA is a synthetic analog of xanthoxylol which has been reported to have similar potent anti-sickling properties.

CLINICAL MANAGEMENT: DISCUSSION

DR. RANNEY: We have time for one or two questions.

DR. SULLIVAN: I wonder about your comment that the prenatal diagnosis of sickle cell anemia is still experimental, that this has been the experience of the Washington group and the San Francisco group. I was under the impression that the San Francisco group was quite enthusiastic about it.

DR. RANNEY: That is right. Our comment that it is experimental was related to the fact that there is a relatively small number of places that have developed the techniques necessary to obtain the fetal blood sample which has to be used. Considerable experience is also needed for reliable chromatographic separations of small samples in which the beta S chain will be present in small proportions because most of the hemoglobin being synthesized is hemoglobin F. We have to have a reasonable amount of experience before we can form an opinion about how widely it can be reliably applied.

It should also be pointed out that some of the patients who had placental punctures subsequently experienced premature labor and spontaneous abortions. In some patients, premature labor would not have been observed because the patients were already scheduled for subsequent therapeutic abortions. We need more data before we can accurately define the risks involved. Prenatal diagnosis is possible, but its risks remain to be established.

QUESTION: Do pregnant patients with sickle cell anemia have increased fetal hemoglobin?

DR. RANNEY: The observations cited were made on normal women who had an increase in fetal hemoglobin during pregnancy. The increase is small and the cells are demonstrated with an anti-hemoglobin F antibody. I do not know whether such increases have been shown in women with sickle cell anemia who are pregnant. Many of the patients with sickle cell anemia who have become pregnant are transfused and observations on circulating hemoglobin F would not be reliable.

QUESTION: Do patients with megaloblastic anemia have increased hemoglobin F?

DR. RANNEY: Yes, they may have 5 percent or 6 percent hemoglobin F. High values of hemoglobin F in megaloblastic anemia are uncommon. In many patients, the duration of megaloblastic erythropoiesis is uncertain. So while they do have megaloblastic erythropoiesis and an expanded marrow, the degree of expansion is probably variable and less than in hereditary anemias. In myelofibrosis, marrow expansion can be considerable and increased fetal hemoglobin may be seen. Myelofibrosis is such a variable disease that it is difficult to draw conclusions.

Fibrosis is also present in the marrow in addition to expanded erythropoiesis. Weatherall's model may not explain all of the acquired increases in hemoglobin F, but it is a major contribution to our perception of the meaning of observed increases in circulating fetal hemoglobin.

Increased proportions of hemoglobin F result from the selective destruction of the cells that do not have hemoglobin F, together with the increase in erythroid clones. But attributing increased proportions of hemoglobin F to these two mechanisms may be an oversimplification, for example, in a group such as the Saudi Arabians that has been observed as having 30 percent fetal hemoglobin, even in patients with quite well compensated sickle cell disease.

DR. RANNEY: Before closing the discussion I would like to emphasize two points regarding the general management of sickle cell crises. There is an increasing recognition of the association of infections of various types with crises, and infections should be considered as a potential precipitating event for crises. Second, hydration is a very important therapeutic maneuver. Dehydration occurs readily in patients with sickling because they do not concentrate urine as do normals. Recent studies indicate that the concentration of sickle hemoglobin within the red cell has an enormous effect on the rapidity with which the polymerization of deoxygenated hemoglobin S occurs.

This makes it very important that cellular dehydration be avoided.

In the general management of sickle cell crises, we emphasize the identification and appropriate treatment of infection and the prevention of dehydration as two important measures for treatment.

I would now like to thank the members of our mini-symposium for their informative presentations. Thank you all.

GENETIC COUNSELING

Carl D. Robinson, M.D.
Robert F. Murray, M.D.
David Satcher, M.D.

COUNSELING FORMAT AND PROTOCOLS

Carl D. Robinson, M.D.

What actually goes on in a counseling session has worried a lot of physicians and nonphysicians. Who counsels? Who sets the standards for counseling? Does the physician have the time to counsel? Can these efforts, in truth, be standardized? Defining terms and standardization of counseling is a difficult task. It is more so when we are discussing the inheritable disease process in sickle cell disease. So I will discuss sickle cell counseling from the programmatic standpoint, that is, whether the efforts to standardize or to develop an approach to sickle cell counseling are producing results.

What is sickle cell counseling? Sickle cell counseling refers to the entire process of communicating accurate scientific and medical information to the individual screened by a competent laboratory. This communication allows the client to better understand his hemoglobinopathy in order to make informed decisions regarding his present and future health pattern. The key word is "informed." The communication effort that we call sickle cell counseling also affords the client a mechanism of referral to resources that will assist him in coping with that hemoglobinopathy on a day-to-day basis.

When one looks at the process of sickle cell counseling, one realizes that it is multidisciplinary, involving the genetic, the medical, and the psychosocial disciplines. The genetic discipline involves the dynamics of human interaction and emphasizes information given to the client, rather than directive action on the part of the counselor. Genetics seeks to explain the basis of the hemoglobinopathy and the related risks for offspring. The medical discipline concerns itself with the symptoms, the treatment, and the management of the patient with the clinically significant disease. And the social or psychological aspects of counseling refer to the relevant problems such as financial, legal, employment, educational, and family planning. There should be an effort to provide support to affected individuals and families trying to cope with the problems of real or potential chronic illness.

It is apparent that to provide consistency to the counseling efforts throughout the country, one must recognize that a counseling session has certain ingredients that must be present so the information transmitted is understood and retained. These ingredients include simplicity, repetition, illustration, and controlled emotional objectivity. Simplicity refers to recognizing the objective of counseling as informing clients of test results. The information given to the patient usually is complex, but it must be given in a way that can be understood by persons who do not have a background in genetics.

Definitions should be simple and there should be correction of the language and a determined effort to remove misconceptions. Repetition is always a good method to improve communication. The same information can be presented in several different ways. Illustration is usually done by participation, with active participation on the part of the client. We found the utilization of audiovisual aids such as slides, magnetic boards, and dice to be essential. Controlled emotional objectivity is the removal of value judgment on the part of the counselor, or the bias of the counselor toward the counselee.

To mix these ingredients in the proper proportions and provide the same counseling effort, say, in New York, as in New Orleans, would be utopic. However, if one attempts to set standards for these approaches, one can come up with certain criteria that counseling sessions should provide.

I have listed several items we think are essential to good counseling sessions. For example, there should be a precounseling evaluation and a method of allaying anxiety. There should be a novel approach to counseling that is accurate in content and specific to the client's hemoglobinopathy. Good records and good encounter documentation should be kept. We prefer individual counseling over group counseling. Both medical and social referral sources should be available. And there should be followup for the client; adequate protection of the patient's confidentiality; there should be family screening to provide a more detailed

picture of the hemoglobinopathy; and post-counseling evaluation.

To make these standards functional, the following essential elements must be present in a good counseling encounter. The counseling approach must be voluntary, that is, the client should feel that he sought the information on his own, even though the aggressive outreach impelled him to seek information. The approach should be nondirective and objective, utilizing the principles of controlled emotional objectivity. The counselor should establish rapport. This rapport should make the client, not the diagnosis, the focus of the encounter. And the client should feel the counselor is truly interested in him. There should be a free flow of information, a reciprocal communication.

The fourth ingredient of a successful counseling session is relieving the client's anxiety, with the counselor developing the ability to interpret and perceive the apprehension the client may have. He must be able to interpret the client's question. Obviously, this comes with experience. The client must have a feeling of privacy, be it in a one-to-one session or in a small family group. In each session there must be an atmosphere of confidentiality. There must be a method of evaluation. This is the haziest area of all. How can you tell whether the information was understood? And if it was understood, will it be retained? Is the information accurate; how can it be improved?

Finally, there should be a mechanism of referral and followup. A significant proportion of the counseling session refers to the medical and psychosocial followup. The medical followup includes further counseling and supervision of the patient by a physician who is trained in hemoglobinopathy. Social service referral is made on the basis of the socioeconomic and/or the psychological condition of the patient, or at his request.

In general, then, we can say that sickle cell counseling provides the whole spectrum of health care to the patient. Because of the multiplicity of effort in providing these services, certain standards should be established to respond to patient needs.

EVALUATION ASPECTS OF GENETIC COUNSELING

Robert F. Murray, M.D.

At Howard University, back in 1969 or 1970, we began to try to find some means of evaluating our counseling sessions. These sessions were different from those that had been used in other genetic clinics because we developed our counseling sessions in the context of a general genetics clinic, rather than a sickle cell counseling clinic.

It became apparent, first of all, that we had to be certain that the patients, or the clients, received at least a minimum of background information on sickle cell disease. Many of them were not at risk of having affected children, but it was important that they have some genetic information, some of which Dr. Whitten reviewed with you in his presentation about the disease and the clinics.

We began by developing a 20-item questionnaire. We gave this questionnaire to our clients after counseling, but not immediately after counseling because we were interested in finding out what information they carried away with them, i.e., what they retained, not what they could remember immediately after the counseling session. We also administered the questionnaire because our survey information indicated that all the patients came to us without any information at all. When we asked them two questions, "Who sent you to this session?" and "What do you know about sickle cell anemia and sickle cell trait?" most of the people said, "We don't know anything about the disease at all."

So from the standpoint of sickle cell information, we began from ground zero. We have had to modify the questionnaire because as time has gone by, and as educational programs have spread through the community, we find that people come in with some background information. Also, we now modify this questionnaire procedure as Dr. Robinson suggested -- we give both a precounseling and postcounseling evaluation.

In addition, we are trying to evaluate the effectiveness of transmitting the basic factual information about sickle cell anemia through audiovisual means such as movies, tapes, or slides. Other people have looked at this program, for example, Dr. Ray Antley from Indiana, to see whether people can learn effectively from one or two presentations of audiovisual material.

We were going to offer information on a random basis, that is, offer our patients the opportunity to use either audiovisual aids or personal counseling, but we found that almost no one wanted to have only a slide presentation or movie as the method through which information on sickle cell disease was given to them. People preferred to have the information given verbatim by a counselor. This suggests that people prefer to get their information from another person if they have the choice. We had to offer people the two alternatives in order to get informed consent. Essentially all of the people chose counseling.

We tried a different counseling session format, realizing its shortcomings, where we showed a film to a group of individuals and then gave them a questionnaire after the film was over. We realized this procedure did not simulate the counseling situation, but it did simulate a situation in which we could find out how much information patients retained from the film.

I am going to present, first of all, the results from our counseling clinic where the questionnaire was sent to the home of the individual, about three months or more after counseling. Individuals responded voluntarily, completing and returning the questionnaire to us in a stamped, self-addressed envelope. In some cases, we sent three or more questionnaires to clients to try to get them to respond. In general, people do not like to fill out questionnaires they receive in the mail. But everyone we sent a questionnaire to following the session had agreed to participate in the program. So we had their verbal permission, even though we did not get their written permission, to receive this questionnaire for completion.

Our questionnaire was modified recently, although essentially we are asking for the same general information. We want to know if the

client understands what the sickle cell gene affects, what the gene does, and what hemoglobin is. As Dr. Whitten pointed out in his comments, it is not easy for people to understand what hemoglobin is, although we seem to have found effective ways to get the idea across.

The questionnaire also includes questions on genetic concepts that test the client's knowledge of how sickle cell disease or sickle cell trait is inherited, and what the risk of having an affected child is for a parent with sickle cell trait, that is, when one parent carries the gene and the other does not.

Communication of recurrent risk concepts has been the "bugaboo" of the genetic counselor. It is the hardest concept to get across; the idea of how chance operates and that each reproductive event is independent of all others.

We sent the questionnaire to 244 people and received a 66 percent return. We thought that was a good response, but we have been told by some health educators and other surveyors that it is not a particularly good response. Our response rate is better than we had expected since we thought if we got better than a 50 percent return we were doing pretty well with our particular client population.

The mean score was about 74 percent on those questionnaires returned, the median score being 79 percent, showing that we did not have a lot of people with very high scores, or a lot of people with very low scores. Generally, people were clustered around a mean of 75 percent, which is pretty good. A distribution of test scores shows that they tend to be clustered between 63 and 64 percent correct responses.

We also formulated a mean test score according to educational levels, with and without precounseling evaluation. We administered a brief quiz prior to testing at one stage after we had done some preliminary studies because we thought if we found out what people's deficiencies in knowledge were and focused on them, we would get better results on the postcounseling evaluation tests.

With the exception of people in the college and postgraduate years, there was no significant difference whether we administered a precounseling evaluation quiz or not to find out what people's deficiencies and misconceptions were. College and postgraduate students tend to learn from the precounseling evaluation quiz, whereas persons with a high school education or below do not.

A comparison of some of the test scores earlier in the game indicates that the trends in testing scores remain the same. If you look at the scores of persons with sickle cell trait versus those who do not have the trait, you will see that the mean test score of the group with the trait, on the average, is significantly higher than the group that does not carry the trait. Obviously, this group should be motivated to grasp the information.

There is some difference between the scores of people who are married and people who are single. This is significant because we want single people to use the information, perhaps in considering their choice of mate, although certainly that would not be the most important factor.

Test scores also indicated that persons under 21 years of age seemed to have slightly higher scores than persons over 21 years of age. But the difference is not statistically significant in this sample of approximately 100-plus individuals. There was a total of 107 individuals in all classes. The mean test score was about 75. If you study the grade levels and mean scores of the clients, it appears that, generally speaking, you get a gradient from the lower level of education to the upper level of education.

With the counseling techniques we use in our setting, the better educated a person is, the better he is likely to do on the test. It occurred to us right away that the system we are using, a written test, is something that people with more education are more familiar with. However, when we followed the written test up with an oral quiz, we generally got the same response as on the written test. It is not very surprising that when you are trying to teach people somewhat sophisticated concepts about hemoglobin, genes, and recurrent risks, that persons who are better educated will tend to learn better after, say, one or two exposures to the information.

We have not tested people who are at a lower education level to see how they do after two or three counseling sessions. Theoretically, we ought to be able to bring them up to a higher level of achievement on our evaluation instrument.

We also found a correlation between the counselor's judgment of the client's comprehension, and the score the client actually received on his test. Comprehension level was determined using Dr. Robinson's criteria of feedback, interaction, questions that people ask, and the scores they receive. If the counselor thought the client's comprehension was excellent, the client tended to get a higher response than if the counselor thought the client's comprehension was just "good." But below a "good comprehension" rating from the counselor, there was not much difference between the counselor's expectations and the client's actual test score.

If you do not get an excellent or good response in your counseling session, you might have to assume that the session has been unsuccessful and you should have that person come back for more counseling. Some clients may require special efforts to be successful in counseling. I think Dr. Whitten's visual illustration of some of these principles would be helpful in this situation. We have photographs that we use, but perhaps better illustrations of these principles, say in cartoon form and so on, might be helpful in bridging communication gaps. This is one of the areas that is not only difficult in counseling, but also difficult in education in general. The communication gap is something educators have been wrestling with for years, so I do not feel bad that we have not been able to solve the problem, considering our weak background in educational techniques.

Another problem we had in evaluating the returned questionnaires was that the percentage of people below high school level who returned the questionnaire was significantly lower than persons above high school level. The same is true of the people who come for counseling and screening. Better educated people, those at high school level and above, tend to come for the screening programs on a voluntary basis. We need to do a better job of reaching people who do not have a high school education. The less well-educated person tends to think of information as not being as valuable as people who are more educated may think it is.

When we tried to assess acquisition of information by showing a film to two groups of individuals, junior high school students and college freshmen, and then went through an item analysis of each of the items on the quiz, we got the following results. The film that I am mentioning is a film made by the Job Corps entitled, "Sickle Cell Anemia and Sickle Cell Trait." It is a 25- or 30-minute film that is used to illustrate the basic principles of sickle cell anemia and trait.

After one showing, the test was given to the two groups and we compared the results with the results of our regular clients who did not answer the quiz until two or three months after viewing the film. Because of this time lapse the groups are not strictly comparable. Notice that the college freshmen, in general, did a lot better on this quiz than our regular clients. The junior high school students did the worst.

Some questions, for example, one dealing with the relationship between sickling and oxygen concentration, are very difficult questions. We have now modified some questions because we found that generally, most people did poorly on them, including the medical students who were tested. For example, we wanted to get across the idea that oxygen is the key factor in sickling. The test question relating to this information is badly phrased. It is important in any evaluation like this to ask the question the right way.

In our counseling sessions, we tried to differentiate between sickle cell trait and sickle cell anemia. Fortunately, the college freshmen seemed to understand this concept clearly, as do our regular clients. But junior high school students had trouble understanding this concept. This is the problem that we have found right along with this group.

We try to present the idea that people from different countries besides Blacks have sickle cell anemia. We found that, generally, the question relating to this was hard for people to deal with, particularly junior high school students.

The quiz also included a question asking if

malaria causes sickle cell anemia. We hoped that people would understand malaria does not cause the disease, but that sickle cell anemia does have something to do with malaria. Again, junior high school students in the eighth and ninth grades did not do well on this question.

What is a crisis? We want people to know that sickle cell crisis is supposed to be related to pain. Junior high school students did somewhat better on this question than on others, but we still had somewhere around ten percent wrong answers in the other two groups.

One question asks whether only females can have sickle cell anemia. Clients should know that both men and women can have sickle cell anemia. Oddly enough, the junior high school students did very well on this question. With the regular clients, only a small percentage did not understand the question. That made us feel very good. At least one thing got across to almost everyone, that there is no sex predilection as far as the disease is concerned.

Another question asks about the frequency of sickle cell trait in Blacks. The results on this question surprised us because this is a point that we make very strongly in our counseling. Unfortunately, a large percentage of people misunderstood or could not recall this fact correctly. We also ask what hemoglobin is. People did fairly well on this question. College freshmen did especially well.

We ask whether sickle cell trait is associated with bad health. We were distressed that junior high school students did not do well on this question because we emphasize over and over that people with sickle cell trait are essentially healthy individuals. This point is repeated many times over, à la Dr. Robinson's suggestions.

We tested how well people understood the association between oxygen and sickling. It is a very difficult question. As it is written on the test, it is probably a bad question, which may be the reason why almost 100 percent of our regular clients probably misunderstood it. Junior high school students seemed to do better on this question.

We ask about the fact that sickle cells may obstruct the microcirculation. One out of five of our two good groups still did not understand the concept. We tested people on the genetic aspects of sickle cell anemia, that is, what it takes for you to inherit sickle cell trait. Almost everyone did better on that question than on the others.

We ask whether the clients understood that the sickle cell gene protects against malaria. The response to this question was very distressing because it was much worse than anticipated. We worked hard to improve our communication of this fact to the clients. We even illustrated it by showing a map of worldwide distribution of the gene. But apparently our efforts were unsuccessful.

In another question we tried to determine whether people understood the concept of recurrent risk. Despite all of the maneuvers using dice, diagrams, and flipping coins to illustrate the concept of recurrent risk, 72 percent of the group still misunderstood. College freshmen did not do too badly on this question, although they did not do as well as we had expected.

The results of another test question showed us that even college freshmen do not really understand that chance has no memory. The question was, "What is the chance of the third child having sickle cell anemia if both parents have sickle cell trait?" We added some box diagrams to the quiz for people to fill out so we could see whether the problem might be that they just do not understand how the genes got together.

We asked another question to determine whether people understood that both parents must have sickle cell genes to be at risk of having a child with the disease. The poor results on this question are very upsetting. We think people understand the genetics of the situation from the previous question, but then we learn that they obviously do not. Even though approximately 40 percent of the clients carry the gene, they still do not understand what it means to be a carrier of the sickle cell gene.

We test whether clients think there is a treatment for sickle cell anemia. We tell them very clearly in the counseling session, not once, but at two different points, that sickle cell anemia cannot be cured. Some people still

somehow come away with the idea that sickle cell anemia can be cured. This is certainly something they might wish to believe.

Finally, we ask the group, "Do you have sickle cell trait?" One hundred five college freshmen -- who had not yet had sickle cell tests -- saw the film, completed the questionnaire, and answered "no." The responses they had to choose from were "yes," "no," and "don't know." We expected everyone to say they did not know. They all said "no," which reinforces the concept that I have had, and that others have had, namely, that when people come in for testing, they expect the test results to be negative. They are going to be anxious when you do tell them they carry the sickle cell gene, and this reaction is going to significantly influence the counseling situation. This is one of the reasons why I have strong feelings against trying to counsel people at the time you deliver the test results to them. You are going to waste a lot of time in counseling because the clients are just not emotionally ready for counseling. They are trying to cope with the fact that they carry the gene. You have to give them time to assimilate and adjust to that fact before you start giving them the information about sickle cell disease.

THE DIMENSION OF SELF-CONCEPT IN SICKLE CELL COUNSELING

David Satcher, M.D.

Eighteen months ago we reviewed our experience with sickle cell counseling. We were particularly interested in all the areas of concern that clients had revealed by their questions, their responses, and their actions. We also reviewed pretests to determine the areas of greatest misunderstanding in sickle cell education and counseling. After careful review, we determined that all of the issues fell into one of three broad areas: risk in reproduction; personal health prospects, including physical, emotional, and social interactions concerning employment; and insurance and interpersonal relationships. We felt it would be of advantage to concentrate on these three areas, both in our training programs and in counseling sessions. We labeled these areas, "The Three Dimensions of Sickle Cell Counseling: Heredity, Self-Concept, and Social Relationships."

These areas are expanded in the outline below:

Three Dimensions of Sickle Cell Counseling

I Height -- Inheritance Pattern

A. Sickle Trait (AS)
1. Define inheritance -- lack of control
2. One gene for sickle hemoglobin from one parent
3. Chance of passing a gene for sickle hemoglobin to his/her offspring
4. Sickle cell risk for offspring depends on genotype of mate, for example:

AS X AA or AS X AS or
AS X SS or AS X AC

II Breadth -- Self Concept

A. Sickle Trait (AS)
1. This is the carrier state of sickle cell anemia and other forms of sickle cell disease (explain).
2. It is not expected to cause illness and is consistent with a normal life expectancy.
3. May be valuable to have in areas of P. falciparum malaria.
4. Sickle trait cannot change to sickle cell disease.
5. On rare occasions, some individuals with sickle cell trait may have blood in the urine. A physician should be consulted for evaluation.

III Width -- Interpersonal relationship

A. Sickle Trait (AS)
1. Can only be transmitted through reproductive inheritance, not contagious.
2. Who is affected: 1/2 Blacks in U.S.A.; found in whites and other races -- worldwide.
3. Genetic defects are common.
4. Employment and insurance: sickle trait should not be considered as a medical problem; if so, consult physician or counselor.
5. Relatives: At increased risk and may want to be tested.

All of our counseling sessions begin with the counselor making an effort to determine what major concerns the counselee has upon receiving test results or the diagnosis of sickle cell trait (AS), hemoglobin C trait (AC), or sickle cell disease. The counselors are asked to record very clearly what these concerns are, how the counselors deal with them, and how the client responds. In my preparation for this discussion of the dimension of self-concept in sickle cell counseling, we randomly selected 50 charts from our counseling file to review the areas of major concern that patients had expressed. We wanted to know, first, how often the expressed concern fell in the dimension of self-concept, rather than in the areas of heredity of social relationships. Second, we wanted to know the specific nature of the concerns that fell in each of these areas and what implication they would have for our counselors' training program and for our evaluation efforts that are now under way.

Method

To get a random distribution of charts in time and over different counselors, we decided to pull the charts alphabetically. This way, the charts tended to randomly distribute over the last three years and three different counselors. However, one counselor coordinated the counseling effort and had counseled more than 50 percent of the clients. Next we reviewed demographic data on clients, their lab test results, the family history form, and the counselor's record of the session.

Outcome

Of the 50 clients reviewed, 42 were persons with sickle cell trait (AS), seven had hemoglobin C trait (AC), and one had sickle thalassemia (see Table 11). Of the persons counseled, 26 were women either single, separated, or divorced

Table 11. Hemoglobin Types of 50 Counselees

TYPE	NUMBER	%
AS	42	84%
AC	7	14%
S-Thal	1	2%
TOTAL	50	100%

Table 12. Counseling Sample Characteristics

PERSONS COUNSELED	NUMBER	%
Women: personal test	26	52%
Mothers: children's test	10	20%
Couples: personal/family results	8	16%
Men: personal results	4	8%
Fathers: children's results	2	4%
TOTAL	50	100%

Ten mothers were counseled about results in children. Eight couples were counseled about personal and family results, four single men were counseled, and two men were counseled about results in children (see Table 12). Five of the counseling sessions took place in the home, the others in our office. The major areas of concerns expressed were as follows (see Table 13):

Table 13. Categories of Concerns

MAJOR CONCERNS	NUMBER	%
Self Concept	36	64%
anxiety/personal health (14) anxiety/child's health (14) present illness (8)		
Heredity	7	12%
(risk in reproduction)		
Social Interactions	5	9%
(Employment risk)		
History of Hematuria	2	3%
No Major Concerns	7	12%
TOTAL	57	100%

1) Anxiety about personal health or child's health in clients with sickle cell trait or hemoglobin C trait. Twenty-eight counselees expressed this as their major concern. Questions included: "What kind of illness might I have?" "Will I have to take medicine?" and "Am I going to die?"

In 1974, we were still sending notifications in the mail requesting people to come in for counseling. There was a case where a 19-year-old man with AC became alarmed at having a dreadful disease because he heard that because he was affected, he could not fly, mountain climb, or camp. His parents had also heard that an AC patient could not take medication over 250 mg strength because it would reduce his oxygen level. This was despite the

fact that the letter said that hemoglobin C trait was not a disease and should not interfere with activity.

In 1975, another client received a letter asking her to come in for counseling since her test results were available. In the office she related that she delayed the appointment because a 43-year-old man on her street had died of sickle cell disease and she did not want to know her results for fear that she would die, too. All of these clients were recorded as being significantly relieved after counseling.

2) Guilt feelings about sickle cell trait in a child. Eight parents expressed this as their major concern. "What have I done to my child?" was the tenor of their question. "What will happen to him?" One mother was concerned that her 12-year-old daughter's asthma would be exacerbated by the sickle cell trait.

3) Desire to attribute illness to sickle cell trait. Eight persons fell into this category. All of them had some definite medical complaints that had not been fully explained. Upon hearing they had sickle cell trait, their major concern was that it was the cause of their medical problem. These problems included leg cramps, stomach pain, arthritic pain, and one case of a child with asthma. One woman wanted disability benefits on the basis of sickle cell trait as the cause of her weakness and easy fatigue. All of these clients had extensive medical evaluation without specific diagnosis except for anxiety. Unlike the first group, whose concern about their future health was relieved by counseling, most persons in this group became angry because they could not blame sickle cell trait for their problem. Many insisted that it must be the cause.

4) Genetic risk in reproduction. Seven of the 50 counselees expressed this as their major concern. Most of them were unmarried and welcomed information about different risks with different genotype of mates. Two parents who had already completed their family wanted the information so they could counsel their children. One 54-year-old woman, whose children were all grown, succeeded in getting three out of five of her children to come in for testing and counseling.

5) Concern about activity restriction and employment. Five out of 50 counselees expressed this as their concern. Two of these persons were concerned about what restrictions SC would place on their activities. Three of them were applying for jobs and came to us because they had a positive solubility test and had difficulty with the potential employer once this information was revealed. In each case there was no problem after further testing and counseling of the client. We offered to write letters to the employers, if necessary, but the clients were able to resolve the issue with their own information transfer.

6) Hematuria with explanation. Two persons had blood in their urine and were evaluated by the urologist at the Martin Luther King Hospital. No evidence of disease of the urogenital tract was detected. The two concerns expressed were: 1) "Do other people with sickle cell trait have this problem?" and 2) "What is the prognosis for the future?" We answered this question based on our own experience over the last three years. Hematuria seems to be more common in persons with sickle cell trait but it is still considered relatively rare. The prognosis is usually good although the hematuria could recur.

7) No major concerns. Seven out of 50 persons felt they understood sickle cell trait or AC and could explain it.

Summary of Concerns

Out of 50 counseling sessions reviewed, counselees expressed concern about their health as related to sickle cell trait or hemoglobin C trait. Eight out of 36 persons had medical complaints and wanted to attribute them to sickle cell trait. Eight parents expressed guilt about their children having sickle cell trait. Five persons were concerned about their ability to carry out their usual

activities or to get employment. Two persons had hematuria and wanted information about its significance. We labeled the concerns of these 36 persons as self-concept (see Table 13).

Seven persons were primarily concerned about heredity or their risk for having children with sickle cell disease and seven people came to us well informed or had no major concern.

Conclusion

In counseling persons with sickle cell trait and hemoglobin C trait, the concerns expressed most frequently fall into the area of self-concept. The concerns are such that, if they are not properly dealt with, they could interfere with the client's ability to function. In selecting and training persons to provide sickle cell counseling, this concern for self-concept should be strongly considered and dealt with.

GENETIC COUNSELING: DISCUSSION

DR. BOWMAN: I have two or three comments. Number one, I think Dr. Murray and Dr. Satcher have both confused education and counseling. They are two different things. I do think there are very important differences between education and counseling. I think that a distinction will have to be made, clearly delineated. That is problem one.

DR. SATCHER: I would like to respond to that statement because I think the difference is not absolute. Education is certainly a part of counseling. And in terms of counseling, as I see it, the only difference is when we say counseling, we are talking to someone whose test results we know; we are talking to that person specifically about his situation, not about sickle cell trait in general, as in the case of pretest education. And when we educate somebody before counseling, we are talking objectively about what sickle cell trait is, what the risks are. When we have the client's results, and we are talking to him about his own risks specifically, it becomes counseling.

I tried to point out that there is a pretest that we give that is followed by education before testing. I see this as totally different from counseling. I tried to point out that the difference is in counseling sessions, in which people are responding emotionally, in part, to their own self. That is why we entitled this dimension, self-concept. The clients know their test results; they are responding to being told, "You have sickle cell trait." That is different from saying to a client, "When a person has sickle cell, this is what happens." If I tell a person that people with sickle cell trait do not get an illness, he may say, "Well, I understand that." Then I say to him, "You have sickle cell trait." And he comes right back and says, "I am worried about being sick." That is the difference.

QUESTION: I appreciate that you are both very much aware of the sensitivity of the situation. I think that in any kind of situation where people have an abnormal trait, it is anxiety producing. Perhaps we could have a second counseling session where the client has a one-to-one relationship with the counselor and is able to use the information.

DR. SATCHER: That is exactly what I was talking about. Now, the pretest education is not necessarily done on a one-to-one basis. All of our counseling is one-to-one, unless we are dealing with a couple or a family.

QUESTION: Would the clients get a chance to explore their opportunities and use the information you give them?

DR. SATCHER: Yes. I think that is exactly what we are talking about. We are talking about something that happens sometimes one or two weeks after the testing. But there is a problem with writing letters telling people they have sickle cell trait. I think this is something that Bob may want to talk about. We found that when we wrote people to tell them they have sickle cell trait, 50 to 55 percent of them came in for counseling. When we wrote them and said, "We have your test results," 85 percent came in for counseling (in the last year and a half). Prior to that, we had a problem. I am worried about those people who do not come in. I think they are the ones who feel there is a threat to their health.

DR. MURRAY: Jim Bowman had a couple more points he wanted to make before we move on to other questions.

QUESTION: My question refers to education and counseling. I think you have the points to define education and counseling, but I don't have any.

The second point that was made, which I think is very important, is that there is a tendency to repeat things when you know in fact there is very little basis for them. We all have our problems but I do think we have to be honest. And we use the term, "nondirective counseling." We have a tendency to use this term, but we must admit, and studies have shown, that in this type of program counselors do have bias because they are human, and all humans have some bias. There is no such animal as nondirective counseling.

DR. ROBINSON: I think you are absolutely right. "Nondirective" in the context that I am using it refers to counseling directed toward the client, not directed toward the client making a particular decision. That is, we are client-centered.

QUESTION: There is a third question I have, directed to Dr. Robinson again. I would be very much interested in the standards screening and education clinics have developed. What worries me at this stage of our knowledge is, how do you develop a standard? I have seen nothing in writing or in publications showing how you establish the validity of a standard for counseling and education, and whether or not we should all be doing the same things.

DR. ROBINSON: No. What we are doing is developing what we feel to be reasonable criteria of program approaches through testing, that is, through objective questioning of the various clinics and through site visits and so forth. I cannot give you a direct answer to your question. I can say that based on common experience of other clinics throughout the country, and based on common experience from individuals who are in the counseling area, these criteria are being developed and have been presented for evaluation.

DR. MURRAY: Yes, I think Carl's response is quite an honest one. Number one, to evaluate what you are doing, and to be able to do it in a reasonable fashion, it makes more sense to have many clinics using a similar format. Then you can evaluate the format, as opposed to everybody doing his own thing.

Some of the criteria have come out of a meeting of about ten people, people in the sickle cell program, people in counseling, people outside the sickle cell program who have been involved in counseling for many years, and a sociologist medical educator. This group spent two days reviewing the various formats that were used, and tried to arrive at some consensus on a format that appeared to be effective, realizing that nothing can be 100 percent absolute. We are not saying that this one way is the only way to counsel. We are just presenting one way of counseling. There are several ways to counsel, and each counseling approach has its advantages and disadvantages.

I hope that people understand that we are not preaching any gospel for counseling, we are merely suggesting a direction that can be taken. We hope that the best counseling approach will spring from our efforts, or the best way for Los Angeles to conduct counseling sessions, as opposed to Chicago, or as opposed to New Orleans. Second, I want to make the point that the definition of counseling involves education. The agreed-upon definition of counseling by the members of the American Society of Human Genetics involves the communication of facts, which is education. You cannot do any counseling without some education. The amount of education in counseling will diminish as the people who come in are better educated, but there will always be some educational aspects of genetic counseling. I am going to take the chairman's prerogative, and hopefully we are not going to get into a debate on definition of terms. I do not think it will lead to any fruitful decision. The most important thing is to know what the processes involve. That, I think, is what is more important.

QUESTION: I agree with you, because you did distinguish between education and counseling. Counseling includes education. Counseling is the overreaching thing and education is a part of counseling.

QUESTION: Are all of the counselors geneticists? What about the counselors themselves? Who should do the counseling?

DR. SATCHER: My first response is that I do not think anybody has yet answered that question. It was in 1971, I think, that there was a meeting at Cornell University in which six very active geneticists in the country debated the issue of who should counsel. Very interestingly, their main focus was whether the counselor should be the clinician who took care of the patients, or whether the counselor should be the Ph.D. geneticists, who are most familiar with genetics, risks, etc. I think only one person on that panel even entertained the idea that maybe somebody other than those two could be counselors.

When we applied for our sickle cell proposal in Los Angeles, we felt that with all the people with sickle cell trait who needed counseling, there were not enough of those M.D.s who had any training in counseling, or Ph.D. geneticists to answer the need. Second, we did not really feel that M.D.s or geneticists were always the best people for counseling. If counseling is primarily communication, and we cannot train people other than physicians or Ph.D.s to counsel other people, then there is something wrong right there, as far as I am concerned.

So our attempt has been to develop a team. I know that there is some concern about that term. On our team we have a social worker, a health educator, and a community health worker, who has probably been one of our most skilled counselors in followup evaluation.

I think we have to be careful. I think an evaluation is very important before attempting to reach any conclusions. Sensitivity to people's feelings is very important. But most important is communication: how well people can communicate information to other people and be sensitive to other people's feelings and misconceptions.

QUESTION: Somebody spoke this morning about nutrition for the patient. I am wondering if anybody has tried the process of linking up with the Women, Infants, and Children (WIC) program of the Department of Agriculture. It seems to me that could easily be done. In Chicago, this sort of thing is often done by the Board of Health. I am slightly familiar with the WIC program, and I am also familiar with the mass screening efforts on the part of the city health department. The WIC program, I agree with; the city health department mass screening, I have disagreements with. I think the problem is we are not capable of filtering patients into the health delivery system they need, or of giving them the particular information they need.

Second, there is no discrimination in the mass screening efforts on the part of the health department. Certainly in the WIC program, which is geared to pediatrics, there is some question -- which I do not want to get into -- as to whether it is necessary to screen a five-year-old.

QUESTION: My main concern is whether you have a counselor to check people over a period of time. How do sickle cell patients react to peer counselors?

DR. MURRAY: We have not developed peer counselors, but we have experimented with using high school students as counselors. It is too early to say whether it is going to be helpful to try to talk to junior high school students. The reason why these junior high school kids are, in general, doing badly is probably because of a language problem. They are communicating with a different language scheme than we are familiar with, or that the movie uses. So we are going to try to have bright high school students talk to the junior high school students and see whether it makes a difference. We cannot say yet whether it will.

The other possible reason why peer counseling has been unsuccessful has to do with a lack of biological background. The students' knowledge of reproduction may be somewhat shaky, and our educating them helps them to better understand the sexual process and the reproductive process. But I do not have data on this topic. Maybe somebody here has done some work that they could report on.

QUESTION: I want to know whether the counseling is done in the school or in the clinic.

DR. MURRAY: We do our counseling in the clinic. We ask the parents if they have any objections to the child being counseled alone. We prefer to counsel a child without the parents present, if the parents will allow it. Sometimes they will not allow it. We know the students will not talk as freely with their parents present as they will away from their parents.

DR. SATCHER: I just want to comment briefly. We have had some interesting experiences in the area we are discussing. We go to junior high schools and high schools and we educate the class. Then the students are tested -- the parents have to sign a form. As Dr. Murray said, the parents have the option of saying whether they want to be present when the child is counseled, or whether the child can be counseled alone. Sometimes the parents insist on being there.

In one case, a mother insisted on coming by herself and leaving the daughter at home. Of course the mother went back home and translated what we said to the daughter, and the daughter called us saying she did not believe her mother because what her mother had told her was not what she had heard in the education session. The mother had told the daughter she had AS, therefore she should not have any children.

The mother had gone to a counseling session, but in her mind that is what she thought she was supposed to tell her daughter. So I think we have to be aware that there are some dangers, especially when counseling parents of affected teenagers.

DR. MURRAY: In closing, we have attempted to provide you with an overview of genetic counseling, some approaches and their ramifications. We appreciate your interest and participation.

EDUCATIONAL TECHNIQUES

Naomi Chamberlain
Claire Hurst
Cynthia Kaufman
Thomasina Holmes

EDUCATIONAL TECHNIQUES

Naomi Chamberlain
Claire Hurst
Cynthia Kaufman
Thomasina Holmes

MS. CHAMBERLAIN: This hour of educational presentations is designed to demonstrate some approaches that are suitable for teaching health education to audiences whose formal training is less than high school level. These presentations can be done by persons whose primary training has not been in either the field of education or the field of health.

The need for these kinds of presentations has been obvious to those involved in programs for "the community at large." If health information is to reach the public, more people must become involved in the dissemination of information. Increasing the number of information givers also provides participants with an opportunity to raise their performance skills. "Learning by doing" is a basic precept for effective education.

Educational programs are sort of like heaven -- everybody that is talking about education isn't really educating. But there are some important reasons for stressing education in this program. On the national level, the sickle cell disease program can provide a model for other national health programs that say their goal includes "reaching the public or community." National programs on heart, lung, diabetes, glaucoma, and birth defects could well use some of the techniques developed on a national level in the sickle cell program.

MS. HURST: It is just as important for educational programs at the local level to be looked upon as models. The use of a clinic or center, or other programs concerned with sickle cell disease, is important, too, and often directly related to the effectiveness of the local educational program.

MS. CHAMBERLAIN: Oh, there goes the numbers game again. I get so tired of people saying, "Oh, the program's good if you have got 2 zillion--."

MS. HURST: Now, that is not what I mean. The use of a clinic or a center, or any other type of program directed towards sickle cell disease, and the direct relationship to the effectiveness of the educational program, includes much more than just numbers. For example, we need to know how people use the available services. Do they use the maximum number of services indiscriminately? Do they use just a few of the services? Do they use them in a fragmented or in a comprehensive manner? An effective educational program will show the user how to get the best yield for his health dollar.

MS. CHAMBERLAIN: Many of the programs we have seen include a great deal of information on heredity, genetic factors, and so forth.

MS. HURST: A great deal of the program time seems to be focused on the genetic portion. All health conditions are not inherited. What do you think about the proportion of time spent on disseminating genetic information?

MS. CHAMBERLAIN: I think it is appropriate and important because it gives us an opportunity to deal with the issue of informed consent. Now that technology has made undreamed of things possible, there has never been a time when the public needs information on informed consent as they do now. To my knowledge, the sickle cell disease program was the first national program to make a concerted effort to train the public in this aspect of health consumerism.

MS. HURST: That is true. But one of the areas I would like to see more emphasis on is teaching about the body as it should function in a healthy state. Some basic knowledge about the body is absolutely necessary. How can you understand an alteration if you do not know how the original dress was designed?

MS. CHAMBERLAIN: This is true.

MS. HURST: It is really difficult to understand why teaching about the body is not given higher

priority. I know how little I was taught about the body or about health.

MS. CHAMBERLAIN: That goes for me, too.

MS. HURST: The body is the one single thing that all of the billions of people on earth have in common. But to be realistic, how do you think we can ever get enough physicians or other health team members to deliver the kind of general health education we are talking about?

MS. CHAMBERLAIN: Who said only a health team could participate? We say that we are training people for health, but actually we talk about illness all the time, or most of the time. What I am saying is that unless thousands of people are involved in disseminating a basic level of health information, how can we go around saying, "The public will not use the information anyway?" How do we know? To reach the public at large, we are going to have to give up some of our prejudices about who can and who cannot teach. We are going to have to start with ourselves and really practice. You know, a musician who really wants to excel practices from five to six hours a day. And yet, people go around wearing the term "teacher" and "educator" who have not taught two hours in the last five years.

MS. HURST: That means seeking new ways of making information available, understandable, and being willing to say that the goal is the important thing, not the person who is designated as the teacher. A title does not automatically confer expertise.

MS. CHAMBERLAIN: All education should be participatory. It should be continuing, and it should be respectfully presented. You know, you do not send the fisherman who lives by the sea to take a message to the nomad who lives in the desert. We need everybody to participate in disseminating health information. Everybody has a different aura of influence.

MS. HURST: We have been discussing the education programs as they relate to sickle cell disease on the national level and on the local level. But let us be specific. What are some of the ways that information can be utilized by persons not specifically trained in either the health field or in the educational field?

MS. CHAMBERLAIN: Let us start by asking Cynthia Kaufman from the University of Bridgeport. Cynthia, do you think that some of the methods you use could be used by persons whose major training is not in education or in health? Do you see a need for a wider dissemination of basic health and health-related information?

MS. KAUFMAN: Absolutely you are perfectly right. This is exactly the goal of those involved in health education all over the country -- to have as many people as possible participate on whatever level in which they have expertise.

MS. CHAMBERLAIN: Cynthia, please tell us the way you introduce the subject of sickle cell disease to a high school or a junior high school group.

MS. KAUFMAN: The way I introduce the subject of sickle cell disease to a high school or junior high school group is through the use of slides. I don't go in and begin to talk about sickle cell disease. I begin by giving them a little overview of the field of genetics.

Most people think that the study of genetics began with Gregor Mendel, who is called the father of genetics. Actually people have been interested in heredity, the study of genetics, for thousands of years. I use a slide of a cave drawing, which shows a series of horses grouped according to the size of their manes, the shapes of their noses, and the amount of their hair. This is really a family pedigree and it illustrates that someone as long ag as 6,000 years ago was tracing family similarities in horses. It was recognized that there were characteristics which were shared by the members of families of horses.

Throughout history certain family characteristics have been noticed. Many men in the Hapsburg family were known to possess a strong, full, rather unattractive lip which came to be called the "Hapsburg lip."

The blood abnormality known as hemophilia, which results from a deficient clotting mechanism, was noticed in many of the royal families of Europe in the nineteenth century. The abnormality has been traced to Queen Victoria. Since royalty married royalty, there were many affected men. This is a sex linked abnormality which is usually passed down from the female and shows up in her sons. Then it is passed down by an affected male to his daughters and

shows up again in their sons. So interest in genetics has been going on for a long time and people have been studying plants and animals as well as man.

When we study genetics we realize that normal traits as well as disease states are transmitted from parent to child. All of the characteristics which make each of us unique have been inherited from our parents. I use a slide that shows a person with pendant earlobes and someone else with attached earlobes. I have attached earlobes, a characteristic which is transmitted as a recessive trait. A recessive trait is one which must be present in two doses, one from each parent, in order to be expressed. Even though I have attached earlobes both of my parents had the more usual, or pendant, earlobes. Therefore, each of my parents must have had the trait for pendant and also for attached earlobes. Since I inherited both recessive traits, one from each parent, my earlobes are attached. This is not a disease state; in fact, the only inconvenience is that I have trouble keeping large earrings on so I have had my ears pierced.

At any rate, this is an example of recessive inheritance and we will see that this type of inheritance, called autosomal recessive, is the same type which we will see in sickle cell anemia, Tay-Sachs disease, and other hemoglobinopathies, which we will talk about in a little while.

Another type of inheritance is known as dominant inheritance. For an example of this I show a slide of a girl curling her tongue. The ability to curl the tongue is inherited in a dominant fashion, which means that it will usually be expressed even if it is inherited in a single dose from one of the parents.

The traits which we express are those which we inherit from our parents, modified by the environment. All of the traits which we possess are transmitted to us in chemical code packaged in the chromosomes which are found in the nucleus of most of the cells of the body. It is now known that human beings normally have 46 chromosomes.

As recently as 1950 Scientific American, which is one of the most popular of the recognized scientific magazines, published an article which was in error. They said that there were 48 chromosomes in the cells of the human body. But it is easy to understand the error because it was not until 1956 that scientists were able to visualize the chromosomes in the human cell so that they could be accurately counted. From that time on, due to this advance and corresponding discoveries of the chemistry of cell mechanisms, the science of human genetics has advanced at a tremendous pace.

To study the chromosomes, some peripheral blood, that is, blood taken from a vein near the surface in the arm, is treated to allow the leukocytes, or white blood cells, to mitose, or reproduce. Then the process is stopped and the chromosomes are photographed and stained. It is then easy for someone who is trained to count the chromosomes, pair them up, determine if they are from a male or female, and determine if the chromosomes are complete in number and in size.

A disease state called Down's syndrome was originally thought to be the result of an extra chromosome 21 or 22. Newer staining techniques have indicated that the abnormality is due to an extra chromosome number 21, so that the affected person has three chromosomes called number 21, giving him a total of 47 chromosomes.

Some abnormalities are due, not to extra chromosomes, but to an inborn error resulting in a lack of a needed enzyme. An example of this is a condition called phenylketonuria or PKU. We now know that this disease state can be prevented by properly controlling the diet. In most states of the U.S., tests are given shortly after birth to detect PKU, so that treatment can be started in time. PKU is inherited recessively. That is, the parents are apparently normal and the child inherits a double dose of the trait, one dose from each parent, and then the disease state is expressed.

Another inherited disease is found in Ashkenazy Jews whose ancestors came from areas of Central Europe. A baby with this disease seems normal at birth, but soon after shows signs of Tay-Sachs disease. By the time the child is three or four or five he will be dead. This is an abnormality of lipid metabolism which is due to a recessive gene. Each parent must be a carrier, although they are apparently unaffected. The child, however, inherited the abnormality from both parents and it was present in a double dose, so the child was affected.

Cooley's anemia, or thalassemia major, is another inherited, recessive disorder which results in a defect in the amount of hemoglobin present. When each parent is a carrier of this recessive trait, no matter how many children they have, there is one chance in four that the child will be affected by inheriting the trait from each parent. This one in four chance occurs each time there is a child conceived.

When we talk about sickle cell anemia we are talking about another disease state which is inherited as a recessive genetic disorder. The sickle cell hemoglobin molecule differs from the normal hemoglobin molecule by one amino acid. This one difference is enough to affect the capacity of the hemoglobin to carry oxygen and deliver it to parts of the body. Specifically, the difference is that glutamic acid has been replaced by another amino acid, valine, in the hemoglobin protein. This is a chance change, called a mutation, which can be inherited. There are many other possible mutations in hemoglobin. For example, hemoglobin C results when glutamic acid has been knocked out of position and in its place the amino acid lysine is present.

I show a slide of a greatly enlarged normal red blood cell. The red blood cell carries oxygen to all parts of the body so that cellular activity, and thus life, can go on. Another slide shows sickle cell hemoglobin that has been deoxygenated. This results in a shrunken cell that takes on a sickle shape. That is what gives sickle cell anemia its name.

Because the different hemoglobins move at different rates, it is possible to separate them out by using sophisticated laboratory methods. This is the choice mechanism for classifying hemoglobins and is used with other methods for detecting the presence of hemoglobin A, or S, or C.

What is the effect of having hemoglobin S in place of A? If a person has the sickle cell trait he is not affected because he has both hemoglobin A and hemoglobin S. Someone who has sickle cell anemia will have no normal hemoglobin but just hemoglobin S. That is the disease state. In times of low oxygen tension, for example, during infection, someone with sickle cell anemia will have less oxygen transported to different parts of the body. Blood cells will become sickle shaped and jam up in the small blood vessels, the capillaries, and cause pain and crises.

But someone with the trait can be expected to have a normal life and be unaffected. Sickle cell anemia is inherited in a recessive manner. That is, the trait must be inherited in a double dose, one dose from each parent, in order for a child to be affected. And as with other recessively inherited states, disease or not, there is one chance in four each time there is a child conceived that the double dose will be inherited.

When both parents are carriers of the trait for sickle cell anemia the possibility is one in four at each conception that there will be an affected child. But there is also one chance in four that the child will have no sickle cell hemoglobin. And there are two chances in four that the child will be a trait carrier, like the parents, and thus be unaffected. So we may say that when two trait carriers conceive a child there is one chance in four of a child with sickle cell anemia and three chances in four of an unaffected child.

The important thing to stress is the fact that in all cases, whether it is sickle cell anemia or any other situation, the individuals concerned must make the final decisions about their childbearing choices. Sickle cell anemia should not be taught as an isolated situation but taught in the context of inheritance, in general, and other disease states.

After the slide presentation there are usually many questions from the students because, by this time, they are relaxed and do not feel threatened by the information presented.

MS. CHAMBERLAIN: We believe that much of the time that is spent in genetic counseling, in medical counseling, and in social work situations is spent explaining what the body is about, what its functions are, and what the organs are. We strongly believe that if basic teaching about the body was done on a very wide scale, it would pay off in terms of the cost/benefit ratio. Each professional who met a client or patient would not have to start at the beginning -- what we are talking about is a basic level of information. If an educational program was ongoing, this kind of basic information could be as applicable to hypertension, to diabetes, to lead poisoning; so that with each national program, you would not have to start all over again each time.

I want to reiterate the fact that we are talking about approaches. In the next approach

Thomasina Holmes will explain how you can use a slide presentation as a pretest. It takes away the embarrassment for the person who cannot, perhaps, read or write as well as somebody else. It makes the presentation a group activity. It gives you a basic point from which you can reinforce learning. If you plan to show those same slides and hand out information, you are then reinforcing what the audience has already seen.

MS. HOLMES: As Naomi mentioned, one way to conduct a pretest is to have a slide presentation, stopping the slide every so often -- perhaps after every two or three slides -- to ask participants to explain or write a sentence regarding the slides. After making a presentation of this sort, you can get an idea of what people really do and do not understand.

A series of slides can certainly bring about thoughts, information and myths. You can determine what you want people to write or talk about. It does not have to be the written work; you can have dialogue, also, using a slide presentation. Slides can always reinforce understanding and reinforce what people know. At the same time, members in the audience will be participating in the learning activity. Children with sickle cell disease have fun, too.

MS. CHAMBERLAIN: This next approach to educational presentations is what we call "kitchen cabinet science." It involves the use of demonstration as an educational reinforcement. People must understand the workings of the kidneys, the lungs, the heart, and the blood to understand how the healthy body functions. If people really understood some of the basic facts in this area, it would be much easier for the public to understand the deviations and diseases. In a kitchen cabinet science demonstration you look around your kitchen cabinet and pick up the kinds of things that are absolutely ordinary and use them to reinforce your point.

For example, let us take the kidneys. We talked about the fact that the kidney acts as a filter, that it is the main waste disposal system, that it is shaped like a kidney bean, that renal is another word for kidneys, or is related to kidneys, at any rate. Now, what could you do, in terms of a demonstration, that would reinforce the idea that the kidney acts as a filter? What kitchen utensils do you have at home in the kitchen that would illustrate this point?

PARTICIPANT: My coffee pot.

MS. CHAMBERLAIN: Your coffee pot; that is a good example. So, if a person understood what a kidney does, then he could understand where and how it runs into trouble. Any other examples?

PARTICIPANT: A sieve.

MS. CHAMBERLAIN: A sieve, right. Anyone else?

PARTICIPANT: Cheesecloth.

MS. CHAMBERLAIN: A cheesecloth? Okay; any of those items. This is what we mean by kitchen cabinet science demonstrations.

In terms of the lungs, what might you use for demonstration that is ordinarily available and does not cost a great deal, to show how the lungs operate?

PARTICIPANT: A balloon.

MS. CHAMBERLAIN: A balloon. Okay. Any other ideas?

PARTICIPANT: A sponge.

MS. CHAMBERLAIN: You get the idea. People like to participate in this kind of program. After the demonstration, you can recapitulate the accurate information.

What we have called the "cinedrama" is our interpretation of how you can use a film to include participation with the audience. We have written a skit to begin where the film ends. The last sentence of the film is, "Well, will you come back and give us a counseling session?" It is at that point that our skit begins.

The information that was presented earlier by Cynthia is going to come up again in the drama. What we are doing is reinforcing information. Let us say that you have about one hour for the presentation. There is no reason why you have to stand up and talk for an hour, or show slides for an hour. The approach could be varied. Part of it could be a demonstration, part of it could be a dialogue, part of it can be a short film -- any film you want.

You can make up the kind of skit that you want. Using these varied approaches you will have, say, five or six different activities reinforcing the major point that you are trying to get over all in one hour.

You could also use the cinedrama form to train workers. For example, make a check list for the group to use in identifying various emotions and attitudes they thought they saw in the film, or that they would put into the script if you had them write a script. You might have them rewrite a script, to find out what kinds of things they feel are important. By keeping a copy of such scripts, those written by your group at the beginning of their training, and those written at the completion, and those written after a year, you will have some very excellent information in terms of growth, direction for comparisons, or for evaluative purposes.

As an exercise in teaching a group how to identify goals one might say, "Look at this film. What do you think the goals of the film are? Why was the film made? Why use a film instead of a filmstrip?" By asking these questions, you are giving people actual practice in objectively writing goals.

Now we proudly present to you the Hemoglobin Players: Len Hunter of the Ross Laboratories will be Billy Worried; Mark Whitlock of the Yeatman Clinic of St. Louis will take the part of Mr. Worried; Mr. Howard Manly, Special Assistant to the Chief of the Sickle Cell Disease Branch of the National Heart, Lung, and Blood Institute, will be Sergeant Sunday; and Claire Hurst, an educational consultant, will be Mrs. Worried.

MRS. WORRIED: (The doorbell has just rung.) Come on in, Sergeant Sunday. I could hardly sleep last night for thinking about this. I didn't sleep a bit this weekend. Remember I told you about Billy; that's my son who goes to law school, you know. I just couldn't bring myself to tell him about it. So he's here, and you tell him.

SERGEANT SUNDAY: Thank you, Ma'am. I'm glad to see you.

MRS. WORRIED: Well, where's the other one? Where's Sergeant Monday?

SERGEANT SUNDAY: He's out on another call about misinformation about sickle cell and other genetically inherited diseases. We have several new families in the area who have moved in from Greece, and he's gone there.

MRS. WORRIED: Greece? He's gone to Greece? Lord have mercy; no wonder my taxes are so high.

SERGEANT SUNDAY: No, no, not to Greece. He's gone right down the street in our neighborhood on Platelet Street, right off of Plasma Avenue.

MRS. WORRIED: Well, come on in and have a seat. Billy? Billy, this is Sergeant Sunday. He's from the Sickle Cell Information Center. Henry, my husband; he's so worried about all this. He always wanted some grandchildren, you know; he's crazy about children. Henry, you better come on out here, too.

BILLY WORRIED: Good afternoon, Sergeant.

SERGEANT SUNDAY: Good afternoon, Billy. Well, I'm certainly glad to see you after I've heard a lot of talk about you.

BILLY WORRIED: Well, if you've talked to my mother more than five minutes, I'm sure you have.

MRS. WORRIED: Henry, this is Sergeant Sunday.

MR. WORRIED: Good evening, Sergeant.

MRS. WORRIED: I'm so glad you could come over here to tell Henry and Billy about inheriting that hemo, hemo . . .

BILLY WORRIED: Hemoglobin.

MRS. WORRIED: How did you know about that? Did they teach you that in law school, too?

BILLY WORRIED: Oh, Mama.

MR. WORRIED: Well, you know that after we took the test -- that blood test, I mean -- you know we found that both me and you had the trace of it.

MRS. WORRIED: Not the trace, Henry; the trait.

MR. WORRIED: Excuse me.

SERGEANT SUNDAY: You know, maybe I should just go back over a few things that we said a moment ago when we were talking about sickle cell.

MR. WORRIED: Well, that's a good idea, you know. I wasn't there when you talked about it the first time.

MRS. WORRIED: Well, I was so upset. When anybody tells you that you gave something to your children, well, I just pushed it on back into the back closet of my mind and shut the memory door.

SERGEANT SUNDAY: Ma'am, why not look at it this way? Everything your children have, you gave them; you and Mr. Worried. Their height -- I see Billy is tall like you, brown eyes like both of you -- favors you a lot, Mrs. Worried. And he certainly inherited your brains; law school, you know.

MR. WORRIED: Yes. Well, on my side of the family we've got some very smart folks.

MRS. WORRIED: And on mine, too.

SERGEANT SUNDAY: Yes, that's what I mean. You got your characteristics from your parents, and your children got theirs from you. One of the inherited characteristics is the kind of hemoglobin you have in your red blood cells. In everybody's red blood cells they have a kind of hemoglobin their parents gave them.

Hemoglobin is a protein substance, and its job is to take oxygen from the air you breathe and deliver it to all cells of the body. Hemoglobin also is what makes the blood red. There are many kinds of hemoglobin; we are all different.

MR. WORRIED: What does all that have to do with sickle cell trait?

SERGEANT SUNDAY: I understand that when you were tested, you both were told that you had AS hemoglobin. That is, that you had sickle cell trait.

MR. WORRIED: Yes, me and Bertha both are, and we thought we were all just fine. We haven't had any real sickness, neither me nor Bertha. I couldn't understand why, if we had this thing, we were perfectly well. People tell me that sickle cell can make some people pretty sick.

SERGEANT SUNDAY: Having the AS hemoglobin is not a sickness. You did not know you even had it until you were tested.

MRS. WORRIED: Well, now, wait just a minute. I have heard the same thing about hypertension, you know. You can have it and not know it. Do you mean to say it's not a real sickness because you might have it and feel okay?

SERGEANT SUNDAY: No, no. That's a good point, however. What I am saying is that many people get sickle cell anemia confused with sickle cell trait.

BILLY WORRIED: Well, this anemia, this sickle cell anemia, does it develop later on? Is that what you're trying to say, that it could show up later?

SERGEANT SUNDAY: No, Billy. Just like the color of your eyes won't change nor your familial characteristics, neither will your hemoglobin type. AS hemoglobin will never develop into sickle cell anemia in your parents. Each time that your mother became pregnant -- well, let's start with you, when she became pregnant with Billy. You are the oldest, aren't you? Let's start there. Since both your mother and your father have AS hemoglobin, sickle cell trait, there was one chance in four for you to have AA hemoglobin, and one chance for you to have two S genes, one from each parent; in that case, you would have had sickle cell anemia. And then, there are two chances for you to have had an A and a S gene; in that case, you would have sickle cell trait, like your parents.

BILLY WORRIED: Hey, wait a minute. You know, I didn't get tested, and I'm not sure I want to know. If the other kids -- well, what did their tests show about hemoglobin?

SERGEANT SUNDAY: According to this, little Bertha has AS hemoglobin -- the trait. And Junior has AA; he has no sickle hemoglobin. And your brother Robert, who was tested in the service, has no S hemoglobin. In other words, he has AA hemoglobin.

BILLY WORRIED: That does it. With my

luck, I'll be the one to turn up with the real thing -- sickle cell anemia. If Bertha has the trait, and Robert and Junior don't, it stands to reason that the fourth one will be me.

SERGEANT SUNDAY: Not at all, Billy. Look at the board. With each conception, there are four possibilities -- four chances. Chance has no memory. With each pregnancy, there is one in four chances to have an AA hemoglobin, two in four chances to have AS -- the trait -- and one chance in four to have SS, or sickle cell anemia.

BILLY WORRIED: Chance may not have a memory, but I do, and I just don't know.

SERGEANT SUNDAY: Each child is an important individual, Billy. The love and caring for each child, regardless of his hemoglobin type, should be the uppermost concern in making a decision as to whether to become a natural parent. You know, I think that sometimes we counselors get so hung up on being sure that the information about the hemoglobin and how it is inherited gets over, that we forget that each family has its own attitudes and goals to deal with.

MRS. WORRIED: Son, you can get the test or not. That's your choice. But just don't let it press on you. Don't start thinking in terms of being less than a man because of the chances about your hemoglobin.

BILLY WORRIED: Mama, I don't know. I've always intended to have children, to be a father. . .

MR. WORRIED: And that means I'll be a grandfather. And let me tell you, son, our doors will always swing on the welcome hinges for any child, no matter what. And just you remember that.

MRS. WORRIED: Of course, Billy, I know you won't be considering anything like that until after law school, right?

SERGEANT SUNDAY: Well, I see this is getting a little tight here. So, folks, I think I'm going to have to be running along. And if there's nothing more that you need to talk to me about, I think I'd better check in at the office where Sergeant Saturday is. But remember one thing -- chance has no memory. But Captain Chromosome does, and since I haven't called in, I'd better make tracks. You have my number, and you can call me if anyone has any further questions about sickle cell trait or sickle cell disease. Keep in touch. Bye-bye.

MRS. WORRIED: Thank you, Sergeant.

MS. CHAMBERLAIN: Thank you, the mighty Hemoglobin Players. I'm sure they're available for bookings.

So, if you have one hour you can have a dialogue or show slides; you can use other kinds of visual aids, have a kitchen cabinet science demonstration, you can show a short film and have your audience participate in reading the script of a play. See how many times we have reinforced the same information within an hour's time? One other suggestion: if you have difficulty in knowing how to state ideas simply, you might take a look at children's health and science books. They can give you some very good ideas of how to phrase ideas and of what information to keypoint. Most books are well written and have been developed with the aid of science advisors.

I want to talk for just a second about the use of lyrics as an educational reinforcement of facts. At the 1974 center director's meeting in Memphis, Charles Blackwell used the phrase, "chance has no memory," as an introduction to a poem that he wrote concerning the need for educational programs. The lyrics are to be sung to the tune of the song, "Thanks for the Memory." This is another method of reinforcing some of the concepts taught in educational programs dealing with sickle cell anemia.

As you listen to the words of the song, you will hear the following ideas. Number one, that chance really has no memory; that all life is a mixture of pain and pleasure; that we inherit different characteristics; that we are all different; that genetic laws do not change; that each conception brings four chances if both parents are hemoglobin-type AS; and that all babies need love and care, whether they are expected, whether they are arranged for -- such as with artificial insemination -- or whether they are adopted. The last idea is that all parents expect their baby to be the very best baby in the world.

In counseling, we should not dwell exclusively on the negative side of caring for a child with sickle cell anemia without

recognizing that parenthood can be a joy. In giving information, we should be sensitive to the dreams and the goals of the family being counseled.

Before one of the major stars from the Hemoglobin Players becomes the major sickle cell singer, I would like to say that perhaps our total philosophy is summed up in a little thing that we wrote that says, "A teacher does not follow a beaten path to wherever it may lead. A teacher seeks a spot untrod, and leaves a trail for those unshod."

We are not trying to give you any set formula to follow in setting up education programs. We are not trying to say ours is the only way. We are trying to leave a trail that you will improve upon.

Now, if you will listen for those ideas, Claire Hurst will sing "Chance Has No Memory," a genetic teaching song.

MS. HURST: Yes, and I wish to apologize to your eardrums in advance. But at the end of just such a meeting, a song could be used. It leaves a sort of refrain. The refrain does linger; we have seen this happen.

Chance has no memory.
It's kind of like a game,
There's pleasure and there's pain.
The things we inherit
May not all be the same.
How different we are.

Chance has no memory.
Genetic laws don't change.
It may seem very strange,
  but with each conception,
The chance is rearranged.
How different we are.

Babies should all have the same things.
Warm love and the good care that love
  brings.
Expected, arranged for, or chosen,
They still bring joy, girl or boy.

Chance has no memory.
Each time that you conceive,
It's normal to believe
That your child is the brightest,
The best the world's received.
Hold fast to this dream.

MS. CHAMBERLAIN: Thank you, Claire. Very good.

As Charlie says, "We got no shame; we'll try anything."

CURRENT RESEARCH

Ronald Nagel, M.D.
John Bertles, M.D.
Howard Pearson, M.D.

MOLECULAR BASIS OF SICKLING

Ronald Nagel, M.D.

I would like to discuss, briefly, some of the structural and molecular aspects of sickling. As you are all aware, the abnormal hemoglobin S arises from a single amino acid substitution in the position 6 of the β chains. Hemoglobin is made by two polypeptide chains, α and β, each one containing over 140 amino acids (see Figure 54). A polypeptide chain is formed by several amino acids attached to each other by peptide bonds.

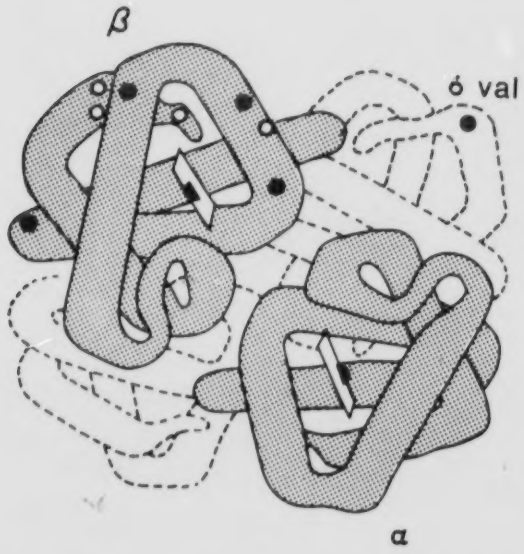


Figure 54. Hemoglobin Tetramer. In black dots, the residues in the β chain that have been shown to affect polymerization. In open circles, the residues that do not affect polymerization. Note that this is not the same β chain that carries the active 6 Val site. (Redrawn from a diagram by Geis in Dickerson and Geis, The Structure and Action of Protein, published by Harper and Row.

The backbone of the chain is composed by the first carbon of the side chain of the amino acid (α carbon) and the C = O and N - H groups. All these atoms form the peptide bonds or amide link. Because of the bond types and bond angles involved, all these atoms are arranged in one plane. So the backbone of the polypeptide chain is a sequence of rigid plates movable only at the level of the α carbon (see Figure 55). What makes one polypeptide chain distinct from another is the order in which the amino acids are placed in the sequence. There are only about 20 amino acids to choose from, each unique in its side chain; to make various polypeptide chains the principal requirement is to put these amino acids in a different order.

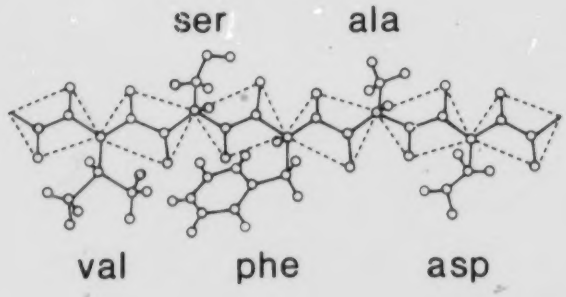


Figure 55. Polypeptide Chain. Five amino acids tied together by peptide bonds.

What makes Hb S different from Hb A is that instead of the glutamic acid, normally found in position 6 of the β chains, one finds another noncharge amino acid called valine (see Figure 56). The main difference between the two side chains is that glutamic acid has a charge carboxylic group (COO^-) and valine has two hydrophobic prones projecting themselves out in the form of a V. This new side chain on the surface of the molecule introduces a new property to the molecule: the capacity of forming long polymers, that is, long strands of Hb S tetramers organized in the shape of a microtubule.

You are all probably familiar with the fact that when red cells containing Hb S are deoxygenated they acquire a shape different from normal; instead of the characteristic round bi-concave disc aspect found in normal cells, odd sickle or holly-leaf shaped cells are induced. When these cells are sectioned and

their interior observed by electron microscopy, the elements responsible for the deformation are uncovered: the long polymers of Hb S shown in Figure 57. These are about 180 Å wide and many times exhibit a paracrystalline array, that is, the center to center distance between the microtubule is constant.

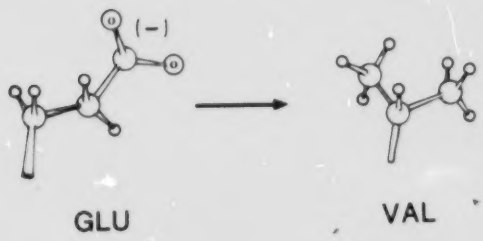


Figure 56. The difference between glutamic acid and valine.

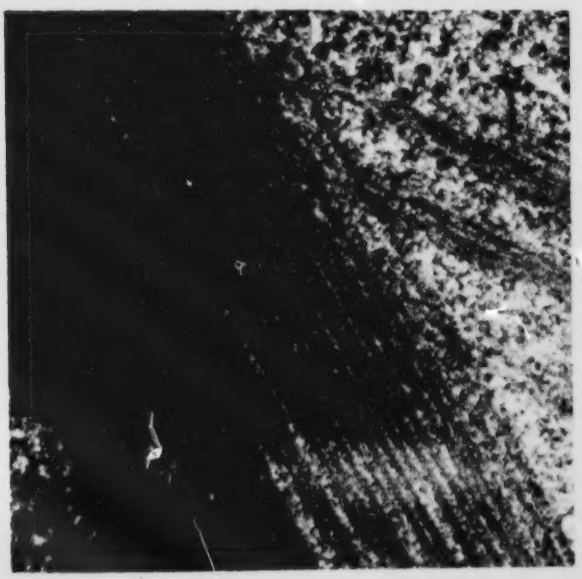


Figure 57. Electron microscopy of Hb S microtubules inside of red cells. Diameter: 170-180 Å. Courtesy of Isabel Tellez, M.D.

The next question is, What are the properties and architecture of the polymer? And very related to the previous question is, Can we design ways to interfere with the formation of the polymer? In order to attack this problem the first thing we have to know is the type of bond that keeps the polymer together.

Dr. Makio Murayama, who now works at the National Institutes of Health, suggested very early that hydrophobic interactions were the principal gluing forces involved. Hydrophobic interactions occur between two protein surfaces when less energy is required to have them in contact with each other than have them surrounded by water. The first clue that hydrophobic interactions were involved came from the negative temperature coefficient of the polymerization, or gelation, of Hb S. This long phrase only means that the polymer needs high temperature to exist (above 10°C generally) and that it is less likely to exist at low temperature. (This is the opposite of gelation, in which the polymer needs low temperatures to gel.)

Danek Elbaum, of our laboratory, has recently confirmed and extended this notion by studying the effect of alkylureas on the polymerization of Hb S. The alkylureas were more effective as inhibitors of gelation the longer the alkyl chain (urea < methylurea < ethylurea < propylurea < butylurea).

Some years ago, Bob Bookchin and I concluded that in addition to hydrophobic interactions other types of bonds probably participate. Working at very low concentrations of salt we showed that gelation (or polymerization) of Hb S was favored. This means that there are some charges on the surface of the molecule that can better maintain the tetramers attached to each other when relieved from counterion shielding.

Finally, we also worked with Hb S in which H ions were substituted by deuterium. The deuterated Hb S showed increased tendencies to polymerize. This can be interpreted to mean that also H bonds participate. In conclusion, the glue that maintains the tetramers together in the polymers is formed by hydrophobic interactions, electrostatic and probably hydrogen bonds.

The next question that needs to be answered is, Why does Hb S have to be deoxygenated to become capable of polymerizing? As you all probably know, when Hb acquires oxygen or other ligands, it changes its conformation. This conformational change involves changes in the tertiary structure (the way each individual chain folds in space) and more importantly,

changes in the quaternary structure (how the two chains array themselves in space with respect to each other). The question was then, Are both changes needed, or only one of them, to turn Hb S into a polymerizing molecule?

Bob Bookchin and I did some experiments some years ago trying to solve this question. We made artificial tetramers in which one of the beta chains or the alpha chains were in the met form (equivalent to the tertiary oxy conformation). The other chains were allowed to become deoxy. The artificial tetramer in which all chains were capable of losing O_2 gelled similarly to the way in which native Hb S does. When the alpha chains were not allowed to deoxygenate (fixing them in the cyanmet form) the tetramer gelled somewhat less readily than deoxy Hb S.

The interesting fact was that the other possible hybrid (β chains in the cyanmet form and α chains capable of deoxygenation) also gelled to the same extent. This seems to suggest that the tertiary structure of the chain (with or without O_2) is not important, and it is the quaternary structure of the tetramer that defines the polymerizability of Hb S. It seems to be an absolute requirement that Hb S be in the deoxy quaternary conformer (T State) for the polymerization to proceed. This notion was further confirmed by Robin Briehl who has been able to gel met Hb S in the presence of inositol hexaphosphate. This mixture seems to be in the deoxy quaternary conformation from a structural and functional point of view.

Finally, the most substantial question is, How is the polymer of Hb S constructed? Or more precisely, What is the supramolecular structure of the microtubules of deoxy Hb S? Several investigators have tried to determine how the individual tetramers arrange themselves in space to constitute a microtubule. By using diffraction of electron microscopy plates, Finch and coworkers have determined the possible structure that is illustrated in Figure 58. This structure is generated by the stacking of six member rings. Each ring is slightly shifted with respect to the underlying one by an angle (called an Azimuth angle) of about 5.8°. This type of stacking generated, of course, a helix in the direction of the polymer axis, which has a very high pitch.

More recently, Josephson in Israel and Edelstein at Cornell, working together, have done diffraction studies of high resolution negative staining electron micrographs and have produced yet another type of structure which is illustrated in Figure 59. Here we have 8 strands, each one beginning with a half molecule offset in the direction of the fiber axis. Again we have a large pitch helix being generated in the direction of the fiber axis. These authors have also found the structure suggested by Finch, but they regard the 8 strand structure as the most abundant under their conditions.

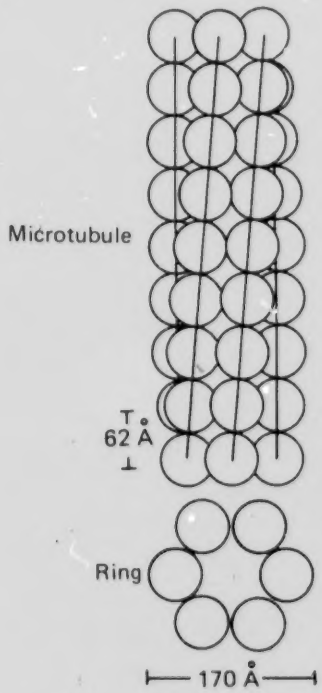


Figure 58. Finch model of the Hb S polymer.

Unfortunately, more research will have to be done to finally establish which of the structures proposed is the one found inside of red cells. If could conceivably be that the microtubule normally exists in more than one supramolecular structure.

The methods quoted up to now are intrinsically incapable of defining which areas of the tetramers are in contact with each other. This is because the molecule has dimensions close to a sphere (65 x 50 x 55) and the orientation of the different axes in each tetramer of the microtubule will not be defined by small angle scattering nor diffraction of high resolution electron microscopy.

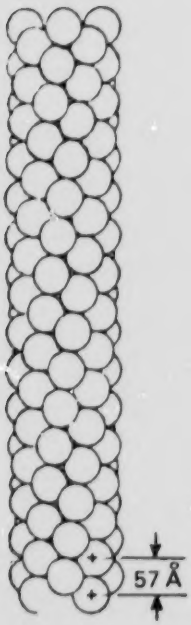


Figure 59. Josephson and Edelstein model of the Hb S polymer.

An additional source of data has resulted from the studies of Wishner and Love of the X-ray crystallography of Hb S. Although this is a high resolution technique, it unfortunately utilizes only the crystal forms of Hb S, not the microtubules. So the information obtained has to be extrapolated to the fiber situation and this is only tentative. We will return to this later.

There is, then, clear need of the input of other methodology for the solution of this problem. Important findings in this connection have come from two sources. First, the use of spectrophotometry of polarized light has been able to establish, in the hands of Bill Eaton and his colleagues at NIH, that the plane of the hemes is aligned with the fiber axis. They have been able to determine that the X axis, the larger pseudo axis of symmetry, is no more than 22° removed from the axis of the fiber. This is an important restriction to any possible packing model.

Second is the use of hemoglobin mutants, single amino acid substitution, in mixtures with Hb S or in hybrids with abnormal α chains. This work was begun about 10 years ago by Bookchin, Nagel and Ranney with the study of Hb C_{Harlem}. ($\alpha_2\beta_2$ 6 Val;73 Asn). An important strategy evolved from the observation that the modification of residue 73 from Asp to Asn, in turn, modified the properties induced by the 6 Val mutation (characteristic of Hb S). This strategy is illustrated in Figure 60.

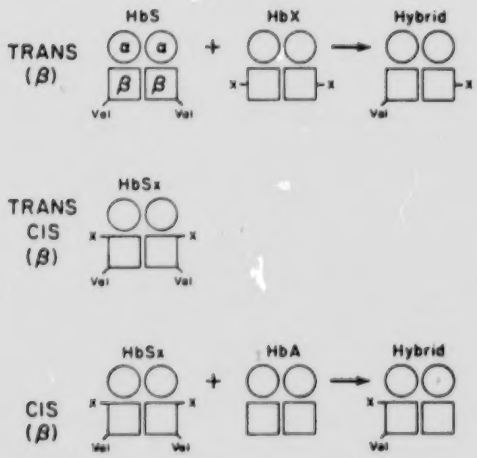


Figure 60. Strategy for the exploration of β chain interacting site in the hemoglobin S polymer. When Hb S and Hb X are mixed, the main specie present is a hybrid in which one of the β chains has the mutation x and the other the 6 Val site. This experiment renders information on trans residues to the active 6 Val site. If cis residues are to be explored, mutants with two mutations in the β chains are required. If the polymerization of the double mutated Hb is altered, further information pertaining to the cis or trans character of the effect can be obtained by mixing the double mutated Hb with Hb A.

At the time of this writing, a number of residues in the β chains have been implicated or eliminated as participants in the areas of contact. In addition to our group, the Krausses in Tennessee have made contributions in the past, and the laboratory of Jean Rosa is now actively engaged in this field. The Beneschs

in New York, using solubility in high tonic strength phosphate buffers, have also apparently implicated a number of residues in the α chains. (See Table 14.)

In Figure 54 we depict in black circles the sites which are implicated in areas of contact; in hollow circles, sites that have been excluded for areas of interaction.

It is time that we return to the results of Wishner and Love from Hopkins. They have found that Hb S crystallizes in a manner so that the tetramers are disposed in a double strand such that its areas of contact complied well with the then available mutational work. It is possible but not necessary that some of the features of the crystal are found in the fiber. Indeed, one can make compatible the Edelstein model and even the Finch model with the double strands of Wishner and Love.

It seems safer at this time to refrain from suggesting which are the areas of contact in the hemoglobin S polymer until the mutational work can provide us with a surface mapping that will make a supramolecular structure, hopefully, unequivocally defined.

Table 14. Current Summary of Mutational Work on the Beta Chains Areas of Contact in the Hb S Polymer

	MUTANT	SITE	INTER-ACTION
TRANS	Deer Lodge	β2 (His→Arg)	No
	C Makassar	β6 (Glu→Ala)	No
	Leiden	β6 or 7 (Glu→0)	No
	G San Jose	β7 (Glu→Gly)	No
	Saki	β14 (Leu→Pro)	No
	E	β26 (Glu→Lys)	No
	C Ziguinchor	β58 (Pro→Arg)	No
	J Cairo	β65 (Lys→Glu)	No
	Korle Bu	β73 (Asp→Asn)	(-)
	D Ibadan	β87 (Thr→Lys)	(-)
	N Baltimore	β95 (Lys→Glu)	(-)
	D Punjab	β121 (Glu→Gln)	(+)
	O Arab	β121 (Glu→Lys)	(+)
	S Travis	β142 (Ala→Val)	No
CIS	C Ziguinchor	β6 (Glu→Val) β58 (Pro→Arg)	No
	C Harlem	β6 (Glu→Val) β73 (Asp→Asn)	No
	S Travis	β6 (Glu→Val) β142 (Ala→Val)	No

*This table contains the work of Nagel and Bookchin, Hassan and Rosa, Nagel and Isaacs-Sodeye, Roth and Nagel, Moo Penn and Nagel, Milner et al., and Charache and Conley.

THE SICKLE CELL IN THE CIRCULATION

John Bertles, M.D.

Some of you may remember a character in a Damon Runyon story who was so powerful -- he was a gambler -- that he would take the dice in his cupped hands, shake them, peep in, and say, "seven," and everybody would say, "Yes, seven." And he would shake them and say "eleven." "Oh, yes," everybody would say, "eleven." The proclamations we make about the pathogenesis of sickle cell disease are analogous to those of the gambler. We may think that the cells are crumpling up as we saw in those pictures this morning. The truth may be, however, that very small, subtle changes in SS red cells, which prevent them from getting through the microcirculation, are at fault in setting forth a wave of problems throughout the body that we call crisis.

One difficulty lies in defining crisis. It has often been said, "The disease a patient has depends on his doctor." I agree with Dr. Whitten; we should try to be very careful in the use of the word crisis. We should be more precise in attempting to describe exactly what is going on. If we lump all problems together into one word, we will be psychologically less inclined to figure out the exact processes in the various organs.

Sickling causes systemic disease; there are difficulties everywhere. It has often been called a "small-vessel" disease, but we all know that difficulties do arise in the large vessels. One of the problems that an SS cell has is getting through the microcirculation, through vessels smaller than the transverse dimension of the cell itself. If a normal red cell has a large area-to-volume relationship, hemoglobin can flow inside the cell until the pliably deformed cell can get through the tiny capillaries. It also must be intuitively apparent that, if a cell can't deform, it is going to cause a lot of trouble.

An oxygenated SS cell that has just come out of the bone marrow often looks just like an AA cell. As deoxygenation proceeds, this cell is going to be in trouble in the microcirculation if sufficient aggregation of sickle hemoglobin molecules occurs. It is not necessarily a stiffly deformed cell that impedes flow -- it could be a cell whose internal viscosity has increased just enough; and, indeed, it might be a cell in which very few of these fibers were present. In fact, it could be a fully oxygenated SS cell which has rattled through the circulation long enough so that water is lost, potassium is lost, and ATP is probably lost. These characteristics describe the so-called irreversibly sickled cell, which actually should be called irreversibly deformed for it remains deformed even when oxygenated. The mean corpuscular hemoglobin concentration (MCHC) of these cells is so high that the internal viscosity may stall them in the microcirculation.

As has been described before in these talks, it is not only hemoglobin S that causes difficulty. Hemoglobin S in combination with hemoglobin O Arab, or with D Punjab, causes the aggregration phenomenon. One has to be alert to this problem in order to determine whether or not the patient is homozygous for hemoglobin S. But does it do any good, really, to know whether the other hemoglobin present is not S? Well, at the moment, it is not going to help the patient. Ultimately, it might have something to do with therapy, and here the work of Nagel and others, I think, is going to be extremely important in sorting this out.

As an SS cell comes out of the marrow, it has several options open to it. Probably, if the proportion of hemoglobin S is high, the cell has a propensity to sickle readily and be taken out of the circulation. If it can make a few passes through the circulation, getting into areas of low oxygen concentration or low glucose, it begins to lose its metabolic capabilities, losing water and cations in the process, and becomes the irreversibly deformed cell I mentioned earlier.

These irreversibly deformed cells have been shown by Dr. Serjeant to correlate in their proportions with the life span of the patient's red cells -- that is, the greater the number of these irreversibly deformed cells, the shorter is the life span tested with chromium 51. It has been proposed that, if there is a single small population of atypical cells in the peripheral blood of an SS patient that

causes trouble, these cells might be it. And yet there does not seem to be a meaningful relation of their absolute proportion in the peripheral blood to the clinical status of the patient. The problem is that we do not know the turnover rate of these cells.

Thus, there are many imponderables in looking at this business of sickle cells in the circulation. My own personal feeling is that we are still some distance from understanding how hemoglobin aggregation affects SS cell function in the human. We do know this: The higher the concentration of hemoglobin in the SS cell, the further the oxygen saturation curve is shifted to the right. And also, we know that the higher the MCHC, the faster the cell becomes stiff as one deoxygenates it, and the more difficult it is for the polymers to dissociate upon reoxygenation.

Yet we really do not understand oxygen delivery and many, many aspects of this disease as completely as we should. The dice are cupped in our hands, but we need better light to read the numbers.

CLINICAL STUDIES IN SICKLE CELL SYNDROMES

Howard Pearson, M.D.

We have heard references this morning to the fact that there is a strong association between sickle cell anemia and increased susceptibility to certain forms of severe infections. These infections include fulminant and frequently fatal meningitis and sepsis, predominantly caused by pneumococci and *H. influenzae* type B. I would like to discuss the epidemiology, pathogenesis, and an approach to management of these serious infections.

Although there are few prospective studies, at least in the United States, to determine the frequency of these severe infections in children with sickle cell anemia, there are some retrospective ones. Diggs, in a retrospective review of autopsy data from Memphis, noted that 25 percent of deaths in sickle cell anemia occurred in the first five years of life.

Watson and Robinson described 16 cases of pneumococcal meningitis in 252 patients with sickle cell anemia, whereas its prevalence in individuals with normal hemoglobin was less than two per 1,000. Barrett-Connor assembled data that indicated that children with sickle cell anemia were 600 times more likely to develop pneumococcal meningitis, and 116 times more likely to develop *H.* influenzal meningitis than children with normal hemoglobin from the same community.

Finally, Powars recently published a longitudinal study of 422 patients from the Los Angeles area with sickle cell anemia. Her data showed that the patients had a relatively enormous risk of developing severe meningitis and sepsis during the first five years of life. Fifty percent of the deaths in her series occurred before five years of age, with a median age of two and one-half years. These infections were also unusual before six months of age, and also unusual after the first five years of life. Thus there is a crucial period of increased risk between about six months of age and about five years of age, when these infections are particularly prevalent. Any discussion of the problem of serious infections in children with sickle cell anemia must address, first, their temporal sequence, and second, their bacteriologic specificity.

There are a number of host defense mechanisms that have been examined in patients with sickle cell anemia to assess their possible contribution to this infectious syndrome. A number of them are not relevant. For example, when compared to normals, the patient with sickle cell anemia appears to have a normal cellular response and an elevated white blood cell count. The metabolic activity of the circulating granulocytes, including their ability to kill bacteria and their reduction of nitro blue tetrazoleum (NBT), appear to be normal.

However, it has been shown repetitively that the process of phagocytosis, the actual engulfing of pneumococci by white blood cells, in the whole blood of patients with sickle cell anemia is quantitatively defective. This defect can be corrected by normal serum, implying a defect in humoral opsonic factors rather than a cellular defect.

A deficiency of heat labile serum opsonins against pneumococci in sickle cell anemia patients was first demonstrated by Winkelstein and Drachmann several years ago. Johnston and his associates have confirmed and extended Winkelstein's observation by showing that defective opsonization is probably due to a defect in the properdin system, the so-called alternative pathway of complement activation.

The properdin system results in the fixation of C3 to the wall of a bacterium. The properdin system does not require antigen-antibody combination for opsonization, but rather is directly activated by bacterial polysaccharides. The properdin system thus does not require antibody for effecting the fixation of C3, the crucial opsonic factor, to the surface of the bacteria and is therefore very important when the patient lacks specific circulating antibody.

However, I should point out that the defect of properdin, this defect of opsonization, is present in older people as well as in children. Therefore, by itself it does not explain the temporal sequence of infection in sickle cell disease. Additional factors must be invoked.

It is our contention that abnormal splenic function is one of the key, important factors contributing to infection. It has long been recognized that the spleens of patients with sickle cell anemia undergo a characteristic sequence of change.

At birth the spleen is not enlarged, but by six months of age splenic enlargement is present in almost all patients. Splenomegaly, sometimes of a prodigious degree, usually persists through much of the first decade of life. Thereafter, repetitive episodes of vaso-occlusion, frequently manifested as severe left-upper-quadrant pain, ultimately reduces the spleen to a siderofibrotic nubbin in the adult, a phenomenon which has been designated as "autosplenectomy." After autosplenectomy has occurred there is true anatomic asplenia.

Some years ago, we commented on an apparent paradox. In the blood smear of young patients with sickle cell anemia, many of whom have enlarged and sometimes enormous spleens, there is evidence of splenic hypoactivity. Specifically, the circulating red cells contain intracellular particles, such as Howell-Jolly bodies. These nuclear remnants are normally removed by the so-called "pitting" activity of the spleen. The circulating blood cells of persons with normal spleens do not contain these kinds of particles.

The development of scanning techniques using radionuclides, such as 99m technetium sulfur colloid, has permitted a direct and quantitative way of assessing splenic reticuloendothelial dysfunction. Scans demonstrate uptake of the radionuclide by the reticuloendothelial system. When done on young children with sickle cell anemia, the enlarged spleen demonstrates a complete absence of reticuloendothelial uptake of the radiocolloid. This has permitted the recognition of what we have called functional asplenia, as opposed to autosplenectomy. Functional asplenia is defined as defective reticuloendothelial activity of the clinically enlarged spleens of infants and young children with sickle cell disease.

We have also shown that, at least during the first four or five years of life, this abnormality can be reversed by whole red blood cell transfusions and is therefore initially a reversible phenomenon. There is a large body of investigative data on animals and on humans that demonstrates the importance of the spleen in protecting against severe bacterial infections. The spleen's role is a dual one involving both antibody formation and clearance of bloodstream organisms.

The person with sickle cell anemia has an antibody response to antigenic challenge that is quantitatively and qualitatively normal when the antigen is delivered by the conventional subcutaneous or intramuscular routes. That is, if a diphtheria toxin or salmonella vaccine is given to sickle cell patients intramuscularly or subcutaneously, his antibody response is perfectly normal.

However, under special immunogenic circumstances clear differences can be shown between the functionally asplenic person and the normal individual. When, instead of using a soluble antigen by subcutaneous or intramuscular routes, a particulate antigen is given by the intravenous route, a clear-cut handicap of the asplenic individual can be seen.

If one gives particulate antigen intravenously and then measures serum antibody, there is a rapid response of antibody formation in the normal individual. When the experiment is repeated with a sickle cell anemia patient with functional asplenia, no antibody is formed at all. When the same antigen is given intramuscularly, a perfectly adequate antibody response is seen, which shows that this is not due to a defect in the antibody synthesizing mechanism. This clearly indicates that the defect is one of the route of administration and type of antigen, rather than a general defect of antibody formation. The same defect is shared by individuals whose spleens have been removed surgically. This response of antibody to intravenous challenge is extremely rapid. Within hours after administration of an intravenous particulate antigen, antibody formation occurs within the substance of the spleen.

If we consider bacteremia, it is clear that in the early stages there is a small amount of particulate antigen which exists intravenously. The sickle cell patient who is functionally asplenic has a handicap because he cannot respond by forming antibody against the bacteria.

A second important role of the spleen concerns its function as a biologic filter with a degree of precision that is unique. When circulating antibody is absent, clearance of bacteria is almost exclusively accomplished by the spleen. This is difficult to show in humans with bacteria, but it can be clearly demonstrated with red cells, as in an experiment by James Jandl.

Jandl took red cells and coated them with varying amounts of antibody, tagged them with ^{51}Cr, and injected them intravenously. He then scanned the surface to see where they were sequestered and destroyed. When the ratio of antibody to red cells was very low, as indicated by a minimally positive Coomb's test, red cells were taken up almost exclusively by the spleen. When the ratio of antibody to red cells was high, and when the Coomb's test was 4-plus positive, the liver became primarily responsible for the removal of antibody coated cells. Therefore, the spleen is crucial for the clearance of particulate material from the blood when circulating antibody is very low or at vanishingly low levels.

How does this apply to the sickle cell patient? If we look at the development of immunity against pneumococci and *H. influenzae* type B as a developmental phenomenon, we can see an interesting pattern. A high proportion of pregnant women have circulating antipneumococcal antibodies. These are gamma G globulins that are passed transplacentally to the baby. This persists for the half-life of gamma G globulin and then decreases to very low levels.

The period of infancy and the first year of life are characterized by very low levels of circulating antibody against pneumococci. Thereafter, through subclinical infections or overt infections, or through nasopharyngeal colonization, antibodies are attained and serum antibodies gradually attain adult level. The same phenomenon can be seen for *H. influenzae* type B antibody. Reasonable levels are present in cord blood, but these fall off to very low levels throughout infancy, and then slowly attain adult values.

The handicaps imposed by asplenia and the lack of circulating antibodies are clearly additive. Clearance of pneumococci from the blood is markedly defective in the functionally asplenic sickle cell patient when compared with either the immune asplenic patient or the nonimmune person with an intact spleen. The patient with sickle cell anemia grows up and acquires a "library of immunity" against *H. influenzae* type B and various pneumococcal serotypes. The importance of the spleen becomes less crucial. This is manifested clinically as a falling off of the frequency of severe and overwhelming infection with *H. influenzae* and pneumococci.

Since clearance of pneumococci from the bloodstream in the nonimmune child is accomplished almost exclusively by the spleen, in the child with sickle cell anemia and functional asplenia, bacteremia might well persist and progress to an overwhelming septicemia with frequent meningeal seeding. This produces an inordinately high mortality rate among young children with sickle cell anemia.

To reduce the inordinately high morbidity and mortality rates of the young child with sickle cell anemia, it is very important that infants at risk be identified as early as possible. In the United States at the present time, the only way to assure nearly complete compliance with testing is to study infants while they are still in the hospital, shortly after birth.

At this time, of course, diagnosis of hemoglobin abnormalities may be a little difficult because the newborn's red cells contain fetal hemoglobin and very little adult type hemoglobin. In infants with sickle cell trait, there is predominantly 80+ percent Hb F, a small amount of normal hemoglobin (Hb A), and a small amount of sickle hemoglobin Hb S. The child who has sickle cell anemia, homozygous hemoglobin S disease, will also predominantly have Hb F, but only sickle hemoglobin Hb S. No Hb A will be present.

Conventional solubility tests and the sickle cell preparations are unreliable for diagnosis of sickle hemoglobinopathies in early life because of the prevalence of fetal hemoglobin. Therefore, the sickle cell prep or the sickledex test cannot be relied upon in early childhood. We have used acid agar gel electrophoresis at pH 6.2 in our studies and have found it very reliable. Microcolumn chromatography is an

equally satisfactory technique. Either technique is suited for diagnosis of hemoglobin abnormalities in the first days of life.

For more than four years, we have routinely performed agar gel electrophoresis on cord blood of Black infants born at the Yale New Haven Hospital. Our aim has been to identify infants with major sickle cell hemoglobinopathies, to anticipate, and, hopefully, to prevent significant morbidity and mortality in the first years of life.

We are not particularly concerned with genetic screening. Rather, we are attempting to identify a population at great risk to provide them with care and supervision to prevent catastrophe.

In our study, we have identified 13 infants with homozygous hemoglobin S disease, and a number with other major hemoglobinopathies. These infants have been enrolled in a special clinic supervised by pediatric hematologists and a pediatric nurse practitioner. We have had the opportunity to follow serial hematologic changes, to determine developmental aspects of splenic function, and, hopefully, to devise ways to change the natural history of sickle cell disease.

Hemolytic anemia was not present in the first month of life but was evident in all babies by six weeks. By 12 weeks, the pattern of hemoglobin level was similar to that seen in older children with sickle cell disease. The postnatal fall-off of fetal hemoglobin was followed. It is considerably slower when compared with the fall-off of Hb F in normal children. However, there is considerable individual variability in the rate of fall-off of fetal hemoglobin. By 20 weeks of age, some children had levels below 20 percent, while in other children the rate of decline was much slower.

Since we believe that the occurrence of functional asplenia determines the onset of the period of greatest risk for severe bacterial infections, this area was carefully studied. We have demonstrated that functional asplenia is not congenital, rather, it is a defect acquired sometime between six months of age and three years of age. In general, this defect develops when fetal hemoglobin falls below 20 percent.

We have found that the onset of functional asplenia is signaled by the appearance of Howell-Jolly bodies in the circulating red cells, and at that point it can be confirmed by isotopic spleen scans. We hope to use the red cell "pit" count by interference phase microscopy as perhaps a more quantitative noninvasive way of assessing this in a serial fashion.

The reason we have performed screening of cord blood is to permit the early diagnosis of sickle cell anemia to identify children at risk and then, hopefully, to prevent serious morbidity and mortality from the early complications of sickle cell disease by providing optimal care. We are not really seeing in our group the "natural history" of sickle cell disease. Rather, we are seeing a "modified history," hopefully, as modulated by good medical care.

Something of the early natural history of sickle cell disease in the United States is suggested by a recent report from Augusta. Ten years ago, a cord blood screening program was carried out to determine hemoglobin genotypes in cord bloods. No special care was provided to affected infants. Twenty-two children were identified at birth as having sickle cell disease but were not provided with comprehensive, continuing care. On follow-up some years later, seven of the affected infants had died -- a mortality rate of 30 percent. The mean age of death was two years.

An important fact is that on the death certificates of three of the seven children, the SS disease was not noted. One can only wonder how many instances of sudden infant death in small Black children are a consequence of sickle cell anemia.

A number of possible approaches can be suggested to prevent the morbidity and mortality of severe infection in infants with sickle cell disease. I would stress again that early identification is crucial. If you wait a year or two to make a diagnosis, half the ball game will be over!

Routine penicillin prophylaxis is frequently suggested for children with sickle cell disease because in most series pneumococci are the most frequent pathogenic organisms. However, in other series, *H. influenzae* are important. The effect of penicillin prophylaxis on these other kinds of organisms is not clear. There are no studies indicating the effectiveness or the lack

of effectiveness of chronic penicillin therapy in preventing severe infections in sickle cell anemia patients.

A case could be argued that if the routine use of penicillin prevented the development of natural antibodies, the period of risk for pneumococcal sepsis might be extended indefinitely. In addition, the problem of compliance is a real one in any chronic disease. Because of these factors, I do not believe that we have sufficient information on hand to permit recommendation of routine use of penicillin prophylaxis in children with defective splenic function or to indicate the duration that such prophylaxis must be continued. Clearly, a controlled study is necessary.

Another possible approach to prevention of sepsis in sickle cell disease might be the routine administration of pooled gamma globulin. We know that children with agammaglobulinemia do not get severe pneumococcal infections. Perhaps a small amount of specific antibody provided in this fashion might be protective. This, however, has not been tried in sickle cell disease.

Active immunization with bacterial polysaccharides is another attractive approach. Polyvalent pneumococcal vaccines against as many as 20 different serotypes of pneumococci, effective vaccines against *H. influenzae* type B, and certain meningococcic strains are available. These could be administered at the time the child develops functional asplenia. Although older children with sickle cell anemia have been successfully immunized with bacterial polysaccharides, the treatment is of uncertain value and probably has an unpredictable value when administered to children under two years of age. Therefore, its value in sickle cell disease may be somewhat limited.

At our institution, we have employed a different approach which could be considered either conservative or radical. Rather than any specific prophylaxis, we have carefully educated our patients' families, provided very close observation, and, most importantly, made available immediate access to medical care provided by physicians who are knowledgeable about the risks of sickle cell anemia.

Families are instructed to bring their children to the hospital when fever occurs or if the child appears ill. Blood cultures are routinely obtained if the child has a fever over 102 degrees, and ampicillin or chloramphenicol is administered.

In our group of infants with sickle cell disease, there have been 35 episodes of significant fever in ten patients followed for a significant period of time. These fevers were usually associated with a probable cause, such as otitis, exanthems, gastroenteritis, or pneumonia.

There have been two instances of pneumococcal sepsis and one instance of pneumococal sepsis and meningitis. One child developed pneumococcal sepsis two weeks after functional asplenia was documented. He recovered promptly after intravenous antibody therapy.

The second serious infection occurred in a 24-month-old child while she was traveling in the South. She developed a fever of 104 degrees. Following instructions outlined in a letter from us, she went to a local hospital. Blood culture and lumbar puncture were done, and therapy with intravenous ampicillin was begun. Both blood and cerebrospinal fluid were positive for pneumococci. The child made an uneventful recovery.

In summary, our clinical studies during the last few years have addressed several points. For example, the optimal time for diagnosis of sickle cell disease is as early as possible, the rationale being the irrefutable goal of preventing morbidity and mortality. Second, I would like to conclude by stressing that unless the kind of comprehensive and continuing follow-up that I have described can be provided, the value of screening cord blood for the diagnosis of sickle cell disease is dubious.

panel

INTERNATIONAL PERSPECTIVES

Graham Serjeant, M.D.

I was a bit concerned with the title of "International Perspectives" until I was assured that it simply referred to the fact that I am from Jamaica. So with that behind us, we will get on to some of the observations that we have been able to make in Jamaica since I first arrived there in 1966, ten years ago.

At that time a sickle cell clinic had been started in Jamaica by Dr. Paul Milner, and was still in its infancy. I went to Jamaica from England with all the well-versed misconceptions concerning sickle cell disease that every good medical student carries: that sickle cell disease is a lethal, lingering, crippling disorder which is associated with chronic ill health and a very shortened life span. Another idea one carried to Jamaica was that survival beyond the age of 30 -- somehow the magic number of 30 seems to have gotten into the textbooks -- was unusual.

I would sit in a sickle cell clinic and somebody would come along to me and say, "I've got this magazine here and it says survival for a sickle cell patient beyond the age of 30 is unusual, and I am 29. What should I do?" The answer, of course, is to ignore the traditional concepts of sickle cell anemia and to look again at what we actually see.

One of the earlier studies we did in Jamaica -- and we are really going back now to very old work -- was a study of elderly sickle cell patients. I refer to this study because we kept seeing patients in it who were 30, 40, 50, and 60 years old. In this study we collected the notes, the names, and the addresses of 50 patients who at the time of the study had been over 30 years of age, and who had not been seen at the hospital for periods of between about five and 15 years. We went out into the country, and of course, many of the patients had moved. We traced them around and this is the result of our study.

Out of the 50, we found five had emigrated. We were not able to find seventeen of the patients, although since then we have managed to trace several of them. Five were dead. But the important thing is that among the 23 patients we located out of this group of 50, 46 percent were alive and relatively well, and living in Jamaica without knowledge of the doctors who had been looking after them.

I said to these patients, "This is very naughty, you missed your last appointment ten years ago." And they said, "Well, doctor, I've got better things to do with my time." So I said, "Look, you are sick. You must not behave like this. You need to go to the hospital regularly. You are having all sorts of problems. What about the pains?" They said, "Look, as I have become older, the pains have become less and less frequent and less and less severe. In fact, since I passed the age of about 30, I have not had a pain. And the leg ulcers I used to have have also healed up. Quite honestly, the quality of life that I have now is better than I have ever had before."

Well, this was a rather startling revelation for a genetic disease, that a number of the manifestations do improve with age, such that patients who were frequently seen in the hospital environment suddenly disappeared. The natural conclusion, of course, was that they had died. But when we did this study we were very surprised to find that they had disappeared from medical observation, not because they had died, but because they had actually improved clinically.

Other work that we did at this time -- and this is still talking about ten years ago -- included a number of fairly comprehensive family studies. One always likes the final flourish in making the diagnosis of demonstrating the presence of the sickle cell gene in both parents. So we used to go out into the country, find the parents, and if we found they both had the sickle cell trait, we would look around at all the other children in the yard -- and there might be twelve other children. We would think, "Well, all these children have parents who have the sickle cell trait so they are at risk from homozygous sickle cell disease." Then we would test the children and find a surprising number of unsuspected cases of sickle cell anemia.

In one presenting case (Figure 61) the patient was 30 at the time of the study. We

followed him since the age of 16 at the university hospital. When we did his family study we discovered that his mother had the sickle cell trait, his father was dead, and we found another brother who was 36, and another one who was 39, both of whom had homozygous sickle cell disease. We asked them, "Have you ever had symptoms? Have you ever had a pain?" They said, "Well, I've had a pain!"

Figure 61. Family pedigree of patient with SS disease. Index case (arrowed) presented with related symptoms. Brothers aged 36 and 39, almost asymptomatic, had unsuspected SS disease.

So you cannot say the brothers were asymptomatic. All one can say is that they have this so-called severe genetic disease, and although they lived relatively close to a hospital, and medical services are generally accessible in Jamaica, the brothers had not had symptoms severe enough to induce them to seek medical attention.

At this time, we had 308 families with 376 patients attending the clinic, and we did these family studies in approximately a third of the families and we found 35 unsuspected cases. You can say a lot of the study patients were young and would get symptoms in due course, but it is interesting that at that time 27 patients were over the age of 12 and some were 30 and 40 years old.

We thought we would try to get as comprehensive a coverage of the patient group in Jamaica as possible. The Jamaican community, outside of Kingston, is often very scattered. This is one of its problems. If you have a patient who has to get up at four o'clock in the morning and walk three hours to the nearest road to catch a bus to get to the clinic by eleven o'clock, where his ears are chewed off for having come two hours late, you will find that patients who are well will not go to the clinic. And so there is a selected defaulting of the benign cases, and the persistence and selection of the severely affected cases. Even in a sickle cell clinic, one ends up looking at the severe end of a spectrum, and a very wide spectrum, that is the clinical involvement in sickle cell disease.

We attempted to solve some of these problems by establishing a series of sickle cell clinics around the island. At this stage we had a group of five clinics outside of Kingston and we used to attend these at about six-week intervals. People who lived in these areas found it easier to come to a local clinic than to travel all the way to the main one in Kingston.

We had a mobile clinical unit with which we would chase defaulting patients. The Volkswagen minibus was extremely good for this. We took all the seats out of the back, and installed a clinical examination couch. We learned early that if you found the patient and said, "Well, now, you must come to the clinic at such and such a date," they often did not come because they had better things to do. So we would just examine them on the couch. We had curtains that went all the way around, and the roof slides back so one can stand up and examine the patient in relative comfort. If we could not reach the patients by car, we tried walking. And finally we managed to get a pretty broad coverage. But all along, there was this tendency for the benign patient to default.

The girls in Figure 62 are sisters. The one on the right, Violet, has sickle cell beta-O thalassemia -- that is basically irrelevant. She has a relatively severe form of sickle cell disease. She was ten years old at the time the photo was taken and her sister next door was eight years old. So we thought, "That is very nice; they are about the same height, so it shows quite nicely the retardation of growth, and the whole sort of change in the physique, the face, the slim legs, and the thin girdles." It was just a nice comparison showing the effects of sickle cell disease in one child compared with her normal sibling. Just to make sure we were not caught, we did a blood test on Myrtle, and Myrtle had exactly the same

condition. So we were back to the drawing board.

Figure 62. Siblings with sickle cell β° thalassemia. Violet A. aged 10 (right) had symptomatic disease. Myrtle A. aged 8 (left) was asymptomatic.

I think what this case illustrates very well within the same family is the whole problem of the selection of observations that have occurred as a direct result of sickle cell disease. Is the real sickle cell disease the chronic problem, with the recurrent pain, the frequent hospital admissions, and the febrile episodes of Violet on the right? Or is the real sickle cell disease reflected by the totally benign condition of Myrtle on the left? Clearly, it is likely to fall somewhere between these two extremes. We realized that all our efforts of attempting to cover Jamaica in this way were not really getting close to the natural history of the disease. So we decided that we must try and get a population where there had been no identification of sickle cell disease on the basis of symptoms, and the best time to do this is at birth.

All you need to do a sickle cell cohort study from birth is a maternity hospital that has an adequate turnover of an appropriate population. Victoria Jubilee, the government hospital in Kingston, handles 75 percent of the deliveries in the Kingston area, and has an annual turnover of between 14,000 and 15,000 babies. It is also one of the most efficiently run institutions in Jamaica. This is very important because what we were asking the staff to do was to collect cord bloods and identify data on all the deliveries that occurred in the ward. You will not appreciate the sort of problems involved in this procedure until you realize that frequently at night there would be three deliveries going on simultaneously with only one nurse on duty.

The technique we used to diagnose sickle cell initially was screening on cellulose acetate. All this work was done by a part-time technician. Every day she would go down to Victoria Jubilee and bring back all the blood samples. We make sure we have the data for the blood and the blood for the data. And then we go through the delivery book to see who we have missed during the previous 24 hours, and then do heel pricks on all the babies we missed. In this way we have had 92 percent coverage of all deliveries at the hospital since the study started on the 25th of June of 1973.

The screening is done on cellulose acetate, but, in fact, as Figure 63 illustrates, they are run from above downwards in the figure, and on each end is an AFS control. The center band, the heavy band, is fetal hemoglobin, and A hemoglobin is in advance of that, so that is below, and S hemoglobin is the faint band behind.

Remember, a baby has a lot of fetal hemoglobin, but the beta-chain synthesis is established, and you can see in the control that that baby has A and S and will develop into a sickle cell trait as the F disappears.

Now, reading from the left, the first one is just AF, so that child is going to be an AA. The next one is AFS, so that is going to be a sickle cell trait. There are then two AF's, and then there is a very faint AFS. We put this in simply to show how variable the degree of beta-chain synthesis is at the time of birth. Next door to that, where there is a heavy band of F, there

is a band of S sickle hemoglobin behind, and then below there is nothing. There is nothing in the position of A. So this is a child that is likely to develop homozygous sickle cell disease. Then we have a series of four who are going to be AA's.

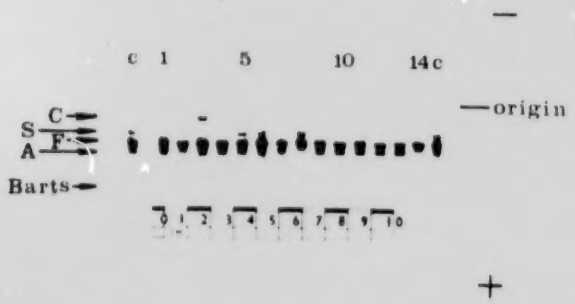


Figure 63. Screening cord blood samples on cellulose acetate. Control AFS samples (c) run at end each of strip. Specimens 1-14 are Barts AF, AF, AFC, AF, AFS, AFS, AF, FS, AF, AF, Barts AF, AF, AF, AFS.

Now, all electrophoretic abnormalities on these techniques -- and we average about 40 babies a day -- are put onto agar gel. My wife has been responsible for the development of an agar gel that is necessary for the numbers that we process.

Figure 64 illustrates fetal hemoglobin, sickle hemoglobin, and hemoglobin A. At the end of each is an AFS control, and there is an AFS control at the other end. The reason we feel an agar is important is there are many hemoglobins that travel in the position of S that are not S.

In our daily collections we built up to a mean of between 30 and 40. The cumulative total is highly predictable, so that present intentions are to screen about 50,000 babies and 100,000 genes. This goal will be reached on April 7, 1977. The point I want to make is how variable the distribution of these sickle cell disease cases is. If we had started this study and suddenly found six or eight cases of sickle cell disease in the first 1,000, we would have been extremely worried about our techniques. And if we had started our study at another point, we might have gone through 1,200 babies without finding a single case of SS disease and we would have been equally worried about our techniques. The message is that in these types of population studies, you need very large samples before you can really draw conclusions.

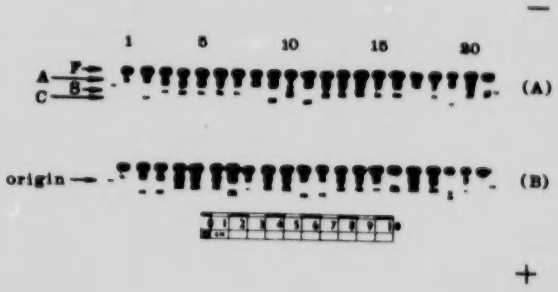



Figure 64. Screening cord blood samples on agar gel.

(A) 3-7 SAF pattern of sickle cell trait.

(A) 2, 9, 11 CAF pattern of hemoglobin C trait.

(B) 16 SF pattern of probable SS disease.

(B) 19 SCF pattern of SC disease.

(A) 10 SAF pattern of sickle cell β+ thalassemia (note disproportionately low level of Hb A compared with Hb S).

(A) 8, 17 AF pattern of other hemoglobin variants which resembled Hb S on cellulose acetate.

Table 15 is an analysis of the results that actually apply to the end of about March when we had tested 32,000 babies, and detected 112 cases of SS disease, 70 cases of SC, and 16 cases of sickle cell beta-thalassemia. The intention of the study was to follow up all cases of significant sickle cell pathology. We follow all SS, all SC's, all S-thal's; we are also following all S variants that we find today, with the intention of documenting the emergence of hematological and clinical features compared to control babies. For every child that has SS disease, we pick two AA controls of the same sex who were born at the same time -- certainly born on the same day, and usually within hours of the index case.

Figure 65 shows some observations we have made. Basically, we follow the babies with appointments every month to six months, every two months to a year, and every three months

after that. Every time we see them, a blood test is done. If this were a venipuncture we would never see the mother of the baby again

Table 15. Analysis of the Genotypes in the First 32,000 Cord Bloods.

GENOTYPE	NO.	%
AA	27,242	85.13
AS	3,273	10.23
AC	1,178	3.68
SS	112	0.35
SC	70	0.22
S-β thal	16	0.05
S/HPHF	3	0.01
S/Variants	2	0.01
CC	10	0.03
C thal	4	0.01
Variants	90	0.28
TOTAL	32,000	100.00

Figure 65. Typical cohort - mother with SS child in center flanked by control babies with normal hemoglobin.

at that stage. So we take all our blood samples by heel prick, and we have had to miniaturize all the techniques we use. But we can get just about all the information that we could from a venipuncture, with the exception of the serum estimations.

Figure 66 shows a comparison of the total hemoglobin levels. These are the results in the first 50 SS's and their 100 AA controls. The open circles are the AA's, and the closed cirles are the SS's. You can see that they very rapidly emerge into two distinct populations on the basis of total hemoglobin, such that you can distinguish them with confidence at the one percent level by the age of two months.

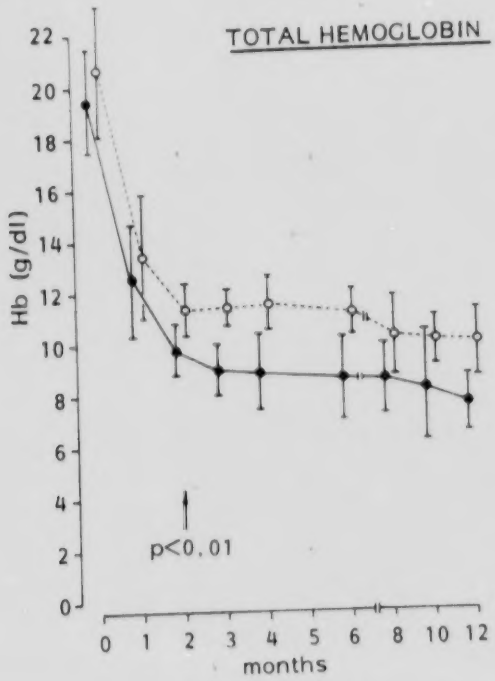


Figure 66. Comparison of total hemoglobin levels in AA (o) and SS (•) infants during the first year of life. Vertical bars represent ± 1 S.D.

Figure 67 shows the emergence of the hemolytic processes gauged by reticulocytes. In one spot, once again, we lost it, but the initial reading is, in fact, not cord blood because that is a useless hematological sample; it is a heel prick done within 24 hours of birth. And then they fall off to levels of between 1 and 2 percent at the age of one month, and then the patterns diverge very rapidly. At the age of two months

there are significant differences at the five percent level and at the age of three months at the one percent level. I have not put the standard deviations in the figure because they are so erratic. There is tremendous variability in the reticulocyte counts of SS disease babies at that time.

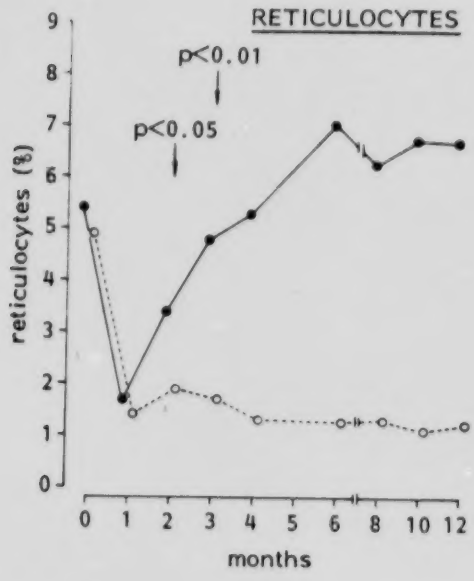


Figure 67. Comparison of reticulocyte levels in AA (o) and SS (•) infants during the first year of life.

Figure 68 shows the pattern of fetal hemoglobin. As to be expected, the decline of fetal hemoglobin is much slower in SS disease. Everybody knew this. It is no remarkable observation. I think what is of interest, though, is the early age at which the difference begins to emerge. And even at the age of one month, it is significantly different at the five percent level; and at the age of two months, at the one percent level. So whatever factors are operative in the slower decline of fetal hemoglobin in our babies with SS disease, they are operative very early on, and probably at a time before the hemolytic process is well established.

What about symptoms? Well, symptomatology, we are told, is unusual before the age of six months, and so I just wanted to point out that we have seen two complications as early as three months: The hand-foot syndrome and acute splenic sequestration at the age of ten weeks. We have seen life-threatening episodes -- indeed, we have seen death from acute splenic sequestration -- before the age of six months, which is before the time at which one would normally begin to suspect a diagnosis of SS disease as the cause of these problems. We have had 18 episodes of acute splenic sequestration in 14 children, with a frequency of ten percent in the first year of life.

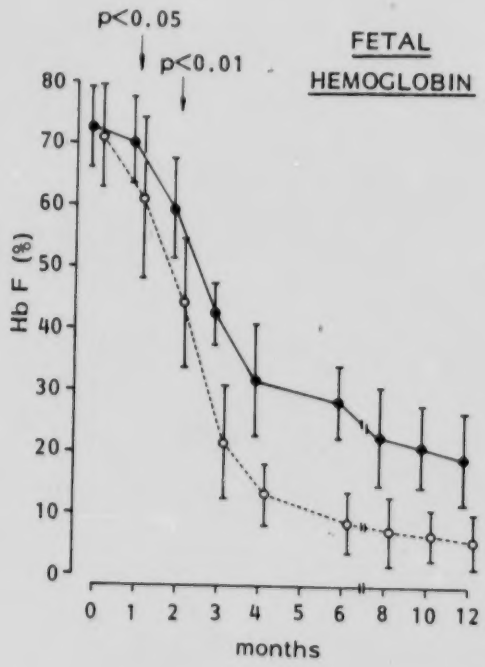


Figure 68. Comparison of Hb F levels in AA (o) and SS (•) infants during the first year of life. Vertical bars represent ± 1 S.D.

Table 16 is a comparison of the clinical features in the first year of life, comparing the AA controls on the left and the SS patients on the right. The numbers are 65 SS's -- do not bother about the figures in brackets for the moment -- there are 65 SS's compared to 139 AA controls. If you look at upper respiratory tract infection, there is no difference; recurrent upper respiratory tract infection, no difference; wheezy bronchitis was more common in SS than in AA, but the difference was not significant because of the small numbers.

Table 16. Comparison of Clinical Complications in First Year of Life.

COMPLICATION	GENOTYPE	
	AA (n=139)	SS (n=65)
Upper resp. tract infection (URTI)	41%	46%
Recurrent URTI	9%	11%
Wheezy bronchitis	4%	15%
Pneumonia	4%	18%*
Gastroenteritis	45%	45%
Malnutrition (Gomez I, II, III)	26%	29%
Anemia requiring transfusion	1%	8%
Hand-foot syndrome	-	15%
Splenomegaly	13%	62%*
Acute splenic sequestration	-	8%
Meningitis	-	2%

*difference between SS and AA significant at 5% level

Then we come to pneumonia which affected 18 percent of our SS babies in the first year of life, compared to four percent of our control babies. That was a significant difference at the five percent level. In gastroenteritis and at various levels of malnutrition, there is no difference between the AA controls and the SS patients. The last group is considered specific sickle cell symptoms anyway so they are all more common in the SS group.

I would draw your attention to the fact that splenomegaly has occurred in 62 percent of our SS's during the first year of life. You think, well that is fine; you would expect that. But 13 percent of our AA controls also had a palpable spleen. So I think it was a surprising finding, and it just shows the need for a control group in almost any situation like this, because unless you have a very clearly documented knowledge of the behavior of children, you have really no background against which to gauge what is going on in SS disease.

As far as the mortality rate is concerned, Table 17 shows that so far we have lost three controls and eight SS's but in the first year of life only seven SS's died. But looking at the causes, we see there is acute splenic sequestration in four. Half of our mortality has been due to acute splenic sequestration. This is in a population where the diagnosis is known, the dangers of acute splenic sequestration are known, and we still have, regrettably, been unable to seriously affect the mortality from that complication.

Table 17. Mortality in Cohort Study

AGE (MONTHS)	SEX	DIAGNOSIS
AA controls		
3	F	Congenital heart disease
4	M	Gastroenteritis
6	M	Gastroenteritis
SS patients		
7	F	Pneumococcal septicemia; acute splenic sequestration
7	F	Acute splenic sequestration
8	M	Gastroenteritis
9	F	Acute splenic sequestration
9	F	Pneumonia
10	F	Gastroenteritis
11	F	Pneumonia
18	F	Acute splenic sequestration

Table 18 is a very preliminary look at the relative mortalities in the different conditions. This is based on very small numbers and short follow-up. But here in the first year of life we see mortality rates expressed per 1,000 live births. Among our AA's it is 19; in our SS's it is 87. So that is four times as great. Our SC's mortality rate per 1,000 is 45.

Interestingly enough -- and these are extremely small numbers, it is really meaningless -- but, we have only lost two cases out of only a small number of sickle cell beta-thalassemias.

Table 18. Mortalities in the First Year of Life Expressed per 1,000 Live Births

AA	19/1,000
SS	87/1,000
SC	45/1,000
S β thal	182/1,000

This study has now been under way in Jamaica for three years. It is our intention to follow this group of patients for as long as is reasonably possible. One can only hope that similar or, indeed, better studies can be performed in other areas to enable the natural history of sickle cell disease to be defined in different areas, and to allow better comparisons for the first time.

INTERNATIONAL PERSPECTIVES

James Bowman, M.D.

It has been stated that in those countries in West Africa in which socioeconomic progress is most rapidly being achieved, sickle cell disease will assume the proportions of a major medical problem. In Ghana, as Dr. Konotey-Ahulu has pointed out, of every million children born, about 30,000 will have inherited abnormal allelemorphic genes for hemoglobin formation from both parents, resulting in disease. Of this number, more than 20,000 infants per million born in southern Ghana have sickle cell disease. And 20 percent of southern Ghanaians and about 10 percent of those living in northern Ghana have the sickle cell gene. About one in three Ghanaians, as Konotey-Ahulu pointed out, has either sickle cell trait or hemoglobin C trait; thus, one in nine matings are among abnormal carriers, with a 25 percent chance of producing children with SS, SC, or CC.

In Zaire the frequency of sickle cell trait ranges from about 16 to 30 percent of the population. So if the frequency of sickle cell trait ranges from 16 to 30 percent in Zaire, about 1.5 to 2 percent of newborns are homozygous for S; in other words, about 15,000 newborns each year have hemoglobin SS. There is also beta-thalassemia in Zaire, and alpha-thalassemia and sickle alpha-thalassemia are also widespread in Zaire.

In a survey in Kinshasa, hemoglobin Bart's was present in about 18 percent of the newborns. Furthermore, sickle cell trait carriers were found with low levels of hemoglobin S without iron deficiency anemia or folate deficiency. In West Africa as a whole, the frequency of sickle cell trait averages about 20 to 25 percent. In the Ivory Coast, the prevalence of sickle cell trait is somewhat lower, about 14 percent, and in Liberia, the frequency is about 12 percent. Of course, part of the lower prevalence of sickle cell trait in Liberia may be because of a European-American admixture, because some of my ancestors were sent back on the boat, not necessarily from whence they came, but to Liberia. In North and South Africa, the prevalence of sickle cell trait is lower than that found in Africa, south of the Sahara.

In East Africa, the frequency of sickle hemoglobin is quite variable, from 0 to 40 percent. In Uganda, the prevalences range from about 0 to 45 percent, depending upon the location. In Tanzania, the frequency of sickle cell trait is about 38 percent, and in Zambia about 13 to 27 percent. I have not mentioned hemoglobin K which is also a high frequency hemoglobin. This abnormal hemoglobin has been described in North Africa and other regions in Africa, including Nigeria.

Now, what about the mortality rate of sickle cell anemia in Africa? Mortality rates are difficult to obtain; even in the United States we do not have good figures on mortality rates. Accurate statistics on mortality rates of sickle cell anemia patients or of morbidity and mortality rates of other diseases are not found in underdeveloped countries, for once such data can be obtained, the socioeconomic infrastructure has developed to the point where the country is considered developed. Thus, accurate statistics are difficult to come by. Nevertheless, most African experts, such as Essan, Isaacs-Sodeye, Konotey-Ahulu, and Boyo, emphasize that there is a direct relationship between socioeconomic status and mortality in sickle cell anemia.

Many years ago it was reported that in Africa, children with sickle cell anemia rarely, if ever, lived past early childhood. But now in some of the more affluent families, the infant mortality rate has been considerably diminished. Probably the most important single factor leading to alteration of mortality in infancy and early childhood has been the introduction of routine malaria prophylaxis for patients with sickle cell anemia, for according to my African colleagues, the greatest cause of death of young infants with sickle cell anemia is falciparum malaria.

At a meeting in Ibadan, in February of 1976, Professor Alan Fleming, who is Chief of Hematology, Ahmadu Bello University, Zaria, Nigeria, reported that he recently did a survey of some rural villages and in areas where the prevalence of sickle cell trait was about 25 percent or more, he was hardly able to find one child past the age of five years of age who had sickle cell

anemia. The high mortality rate of sickle cell anemia in this particular region was attributed to falciparum malaria.

The variability of alpha- and beta-thalassemias and the interaction of these thalassemias with sickle hemoglobin offer important areas of investigation in the hemoglobinopathies. Interestingly, in contrast to what is usually reported in West Africans and in their descendants, the majority of the sickle beta-thalassemia found in children in Zaire is of the S/β° variety.

S/β^{+} thalassemia is also found, but these patients are far in the minority in Zaire. In fact, in Zaire, Professor von Ross, who has done some excellent studies in that area, has only found three unrelated patients with S/β^{+} thalassemia. In Zaire, patients with S/β° thalassemia differ markedly in their clinical picture. Some have severe sickle cell disease with early and pronounced anemia. Others have symptoms like that of thalassemia with intermediate severity. Others are asymptomatic.

In some families in Zaire, Professor von Ross reported so-called benign sickle cell anemia which is associated with very high fetal hemoglobin, about 32 to 41 percent. Hemoglobin F was found to be heterogeneously distributed among the red blood cells. These patients are like those reported in Saudi Arabia who are believed by some to have a combination of homozygosity for hemoglobin S with alpha-thalassemia. (Since this conference, a more recent explanation for mild sickle cell anemia may be found in: Nature, 264: 247, 1976.)

I will skip the rest of the Middle East because I would like to get to some other parts of some other research, particularly that of Essan on hemoglobin Bart's. Now, there is still some controversy in parts of West Africa about the presence of Bart's hemoglobin. Essan has long maintained that in infants in whom he demonstrated a Bart's-like hemoglobin, alpha-thalassemia was not present. But there is no doubt that Bart's hemoglobin and alpha-thalassemia have been accurately reported from Nigeria, Ghana, and the United States. Time will not permit further discussion of this interesting problem.

Recently, I was talking with a friend of mine, Dr. Mehra Khan, who is from India, and is now at the University of Leyden. He told me a very interesting story. Dr. Khan has not reported, but he has studied two castes in India, and in one group the blood of persons with sickle cell trait has the usual 35 to 40 percent hemoglobin S. There is another caste, however, in which all of the members so far have a proportion of hemoglobin S of about 25 percent. It would be most unlikely for alpha-thalassemia to be present in all of the members of this particular population. The reasons for these differences (since there is no duplication of the β chain) are not evident.

West Africans have given considerable attention to the controversy over sickle cell trait and aviation. The debate began over what I term international racist medical politics. According to my African colleagues, several airlines, unnamed, began to spread rumors that, "You should fly on our airlines because, after all, our pilots do not have sickle cell trait and African pilots do have sickle cell trait, and therefore, it is not smart to fly on African airlines." Needless to say, this caused a considerable amount of rancor, and some reputable European scientists also backed up the statements of the Western airlines.

A conference on sickle hemoglobin and aviation was held in Dakar in June of 1974, sponsored by the African Civil Aviation Commission. Two of the most important contributions at this conference were presented by Dr. Addae of the Department of Physiology of the University of Ghana Medical School, and by Dr. Djabanor of the Military Hospital in Accra, Ghana. The report was fairly long, but I will only read the conclusions of the conference. Dr. Addae and Dr. Djabanor reported some very interesting prospective studies on pilots in which they subjected them to tests in pressure chambers and in-flight, and found that the subjects experienced no difficulty. These studies are being continued.

The seminar recommended the following:

"Considering the several hundreds of thousands of sickle cell gene carriers who have flown and continue to fly yearly in both pressurized and unpressurized aircraft at various normal operational heights and in all types of weather;

"Considering the rare incidence, if any, of in-flight or post-flight incapacitation in the above;

"Having reviewed and scrutinized all available literature on incidents of incapacitation or even sudden death which have been associated with the trait and having found no scientific basis to correlate these with the trait;

"Recognizing the pitfalls in diagnosis and the confusion surrounding terminology which previous articles and authors have fallen into;

"Having reviewed available and up-to-date research into the implications of sickle cell trait,"

"That until proven otherwise, the present policy of allowing pilots, cabinet attendants, and what have you, with sickle cell trait, to fly should be maintained, with respect to the African Civil Aviation Commission."

They also recommended that carefully controlled studies be done to disprove or substantiate reports that are replete in the literature.

Well, let's leave this fairly controversial subject for something else that may be even more controversial. I should mention two therapeutic agents for sickle cell anemia, originating in Africa, that have been reported in the scientific literature. These agents have had wide press coverage here and abroad.

First, I will briefly discuss the anti-sickling properties of extracts of the African chewing stick, *Fagara xanthoxyloides*. In 1971, Sofowora and Isaacs, now Isaacs-Sodeye -- he recently changed his name -- found that root extracts of *Fagara xanthoxyloides* inhibit and reverse sickling in vitro.

In 1975, Sofowora, Ogunkoya, and Isaacs-Sodeye isolated 2-hydroxymethyl benzoic acid from the root extracts and found that this chemical prevented sickling in vitro at a concentration of 1 microgram per milliliter. Sofowora's group in Ife has since modified this compound -- and this compound is also being modified in the United States -- in order to find more effective long-acting compounds.

Professor Isaacs-Sodeye reported on the progress of clinical testing of Fagara extracts at a conference in February of 1976 in Ibadan. Professor Isaacs-Sodeye's paper was followed by a long, heated discussion, and most of the assembled scientists felt that there is presently no indication that Fagara extracts are effective in vivo.

It was recommended at the conference that double-blind crossover studies be initiated in Nigeria to determine the efficacy of this agent. It was further emphasized at this conference that until such studies are done, no claims could be made about extracts of Fagara. In fact, many African scientists were somewhat embarrassed by the international publicity given the agent before the conclusion of proper studies. In fact, some of us teased our African colleagues because they have long talked about Americans, the publicity over urea and cyanate and other things, and I reminded them that now the shoe was on the other foot.

It was suggested that possibly the Americans should support research on Fagara. I disagreed on the basis that Nigeria is a wealthy country, Nigerians initiated the problem, and there are more patients with sickle cell anemia in Nigeria than in the United States.

The French pharmaceutical company Synthelabo sponsored an international conference on sickle cell anemia in January of 1975 in Abidjan, Ivory Coast. On the last day of the conference, the reason for the meeting became evident: to present a series of papers on Vincamine, which is produced by Synthelabo. Vincamine and its derivatives have been the subject of a series of reports in the prevention and treatment of crises of sickle cell anemia. At the conference, the Nigerians, Ghanaians, Americans, and most Europeans were not impressed by the reports of the French and the Ivoriens. (Many of the French participants who had not worked with Vincamine were also skeptical.) Claims of the efficacy of Vincamine and its derivatives in the prevention and treatment of sickle cell crises must await proper double-blind crossover studies, which have not been done.

QUESTION: I want to ask Dr. Serjeant about infectious complications. Aren't they a problem in terms of pneumococcal sepsis in this population? I was surprised the patient did not show that as a cause of death.

DR. MAJERUS: There was one who died of pneumococcal sepsis.

DR. SERJEANT: Yes, there was one death associated with acute splenic sequestration. It obviously occurs. We have had one death. We have had four cases so far in the first year of life, all picked up and treated.

I think we were expecting the problems to be more frequent than they have been to date. I am afraid that with mild febrile episodes that resolve very quickly we are not doing blood cultures on every single one. It might well be that we would pick up transient septicemias if there were a more widespread use of blood cultures. But it has been a surprise to us that it is not as common as we had been expecting.

DR. MAJERUS: Dr. Serjeant, it appeared to me that the incidence of homozygous sickle cell anemia was deficient in your prospective study by a significant amount. Can that be accounted for just by fetal loss or fetal mortality? The incidence rate seems awfully high. As I recall, it was 0.3 percent SS with 10 percent of sickle cell trait incidence. Did I misread the slide?

DR. SERJEANT: No. In fact, with the 10 percent prevalence, you would have expected 0.25 percent. What is happening is if you work them out on the basis of gene frequency -- and I have another slide that compares the observed and expected ratios -- they are uncannily close. We have observed 122 cases, and we would have expected, I think, 121.7. So they really are extremely close at the present time. There is absolutely no evidence of intrauterine loss of babies that have the SS genotype.

QUESTION: I wonder if you would comment on the overlap of hemoglobin levels that you show despite the .01 significance. There was quite a bit of overlap between the controls and the other children. Would you care to explain that?

DR. SERJEANT: I really have not got a lot to say about that except that these observations are made during the children's first year of life, and a lot of children become anemic during that time, whatever anemia is.

I think, in many of the parameters of SS disease there is an overlap with the general population. It is just that the means of the groups fall fairly clearly apart. But we certainly have SS babies who at the age of one year have hemoglobins on 10 and 11 grams, and we certainly have AA babies at the same age who have hemoglobins of 7, 8, and 9. I do not think there is any great significance in this.

DR. SULLIVAN: I wonder whether the non-life-threatening complications of sickle cell disease, such as leg ulcers and other similar problems, are as common in your mild sicklers as in the more severe ones. Did you have a chance to look at any of these problems, such as hematuria?

DR. SERJEANT: I think defining the severity of sickle cell disease is everybody's constant headache, is it not? In any sort of therapeutic assessment, in any talk about the natural history of sickle cell disease or in any observations that are supposed to detect variations in it, one constantly comes up against the question, What do you mean by a severe case of SS disease? You can define it easily in terms of hemolysis. You can say this person has a rapid rate of hemolysis and this person has a less rapid rate. That is simple. It is quite different to jump from that to infer that a rapid rate of hemolysis implies a severe form of the disease.

So we have not found the answer to this question, I am afraid. We can say that we have a group that has pains, we have a group that does not have pains, we have a group that has rapid hemolysis, we have a group that has less rapid hemolysis; we have a group that has high hemoglobins, and we have a group that has low hemoglobins.

To come back to your original question concerning leg ulceration, there is no clear-cut

correlation between leg ulceration and hematological and other clinical manifestations which we would normally interpret as indicating severity. Leg ulceration seems to cut right across the board, and it is a very difficult complication to assess in that way. I just do not know what the answer is.

DR. SULLIVAN: Have you had a chance to follow many of these patients when they have come, let's say, to the States, to assess the effect of change in locale on their disease?

DR. SERJEANT: This is a very interesting question, and I shall now speculate. Yes, we do follow these patients. We try to keep in close touch with our patients when they come over, and they are really very good, because they do write to us quite often. We always give them a letter to put them in touch with whoever is appropriate where they are going, of course. And they do keep in touch with us. Whenever they are back in Jamaica, they always come to the clinic and get a blood test for their pains.

But there is no clear-cut pattern of difference in patients who change locale. I can recall a group of patients who have had more frequent and more severe painful crises after going to a cold climate. I think there is no doubt about that at all. But it does not apply to everybody. You can't predict to whom this is going to happen.

I recall one family with SS twins that moved to England, and after having problem after problem with the twins' health, they returned to Jamaica, not because the doctors told them to, but because the mother was convinced the twins' health was much better in Jamaica. And it has been since they have come back. Now, this is anecdotal.

All I can say is that even in Jamaica we find a relationship between temperature and painful crises. This, of course, is looking at relatively small temperature variations, but there is a significantly increased prevalence of crises during the six cold winter months over the warm summer months.

DR. MAJERUS: We all feel better when we are in Jamaica.

DR. SERJEANT: I am not sure that is a controlled observation.

DR. MURRAY: Recognizing that the numbers you have for this first year are small, are you prepared to suggest any hematologic parameters that might possibly turn out to be predictors of those patients who have either died or had serious complications early, say within the first six months or so?

DR. SERJEANT: I am going to say a terrible thing, and that is that we have this information but it has not yet been analyzed. This has been one of our problems over these ten years. The cohort study now involves 500 infants and the adult sickle cell clinic involves approximately 1,500 patients. We have an enormous data bank which needs to be put into order so we can get the answers out. The answers must be there, but I am afraid I can't give them to you at this time. I hope in a year's time the situation will be very different.

DR. MURRAY: In addition, I would like to make one more point about the controls. In addition to the time and place of birth, are they controlled for locale of residence?

DR. SERJEANT: No, Victoria Jubilee serves a relatively homogenous area of Kingston. It is principally the area around the hospital, where the greatest density of population is located. The patients all have a relatively similar socioeconomic status. Obviously there will be variables, but one just hopes that in the bulk of controls, the variables will gradually cancel each other out. It will just be too difficult to make very rapid socioeconomic assessments to select controls because the patient population at Victoria Jubilee turns over so rapidly. The mother stays an average of 30 hours. In that time we have to go down, get the cord blood, get the result, go back to the mother, tell her the answer, tell her what is going to happen, and why you want to follow the baby. If we had to visit their homes and try to make socioeconomic assessments as well, it would be difficult.

But I do not think this will be a major problem because the controls do come from broadly similar backgrounds. If we get a wealthy AA, then we are likely to get a wealthy SS, so one hopes the whole thing will balance out within the entire study.

QUESTION: I wonder if Dr. Bowman might comment on Dr. Konotey-Ahulu's belief that

mild cases, at least in Ghana, are related to socioeconomic status of the individuals. Would you comment on that?

DR. BOWMAN: Well, I mentioned that these are anecdotal reports. I have seen nothing that we could say could be documented. Nevertheless, my African colleagues inform me that patients with sickle cell disease who have a high socioeconomic status come into the hospital less frequently with complications of sickle cell disease.

Africans in general do not like to give their children malaria prophylaxis because it prevents the development of immunity. Thus if malaria prophylaxis is started in early childhood, it would have to be continued until malaria is eradicated in Africa, and this will not be possible in the foreseeable future.

African physicians therefore watch their children very carefully, and at the first sign of malaria they treat them just enough to alleviate symptons so that an immunity is developed. But this cannot be done with sickle cell anemia patients because of the prohibitive mortality of falciparum malaria in patients with sickle cell anemia.

QUESTION: You have been talking about sickle cell disease in relation to malaria. There is a debate in Aftrica as well as in the United States about the relationship between malaria and sickle cell trait. I know you have some feelings about that. Would you discuss it?

DR. BOWMAN: I do not want to burden you with my prejudices. I have written extensively about this. There is no doubt that everywhere sickle hemoglobin has been found, falciparum malaria has been present or is present. There are many studies showing a geographical association in East Africa between endemicity of falciparum malaria and the prevalence of sickle hemoglobin.

Time will not permit more detailed discussion, but I must emphasize an important practical point. Persons who are not immune to falciparum malaria and who have sickle cell trait (and this includes most Americans) should not waltz into West Africa without anti-malaria prophylaxis, because they might not come back alive. Persons with sickle cell trait do develop falciparum malaria, and they can die. And that is very important. As a result of publicity about malaria, I have known persons who have gone to Africa and said, "I don't have a thing to worry about because I have sickle cell trait." This belief can lead to tragedy.

QUESTION: Is there any information in either group of the two castes that you spoke of with the high and low S levels -- is there any information on those two groups or any other groups of the incidence of hematuria in the two?

DR. BOWMAN: No. I have no information on that point.

DR. MAJERUS: Do any of the clinicians in the audience have an explanation for why adults with sickle cell anemia do ameliorate? It does seem clear that the disease gets milder as people get older. Is there any legerdemain of pathophysiology that can explain that?

DR. BOWMAN: I would like to make one comment on it. I was very pleased that Dr. Serjeant qualified his statements, because his initial report on benign sickle cell anemia is often misquoted.

DR. SERJEANT: Thank you.

DR. BOWMAN: And that is bad if you are misquoted, because even in the United States, if we were to select people over the age of 30 with sickle cell anemia and study their clinical picture, the clinical picture would be mild by virtue of the fact they had reached age 30.

DR. MAJERUS: Yes, but it is clear to those of us who follow patients that they often do ameliorate, that they have a lot of trouble as children, and then they get better.

DR. SERJEANT: Maybe I could just add a point. You are quite right. One is frequently misquoted on this point. I keep getting assailed by people at cocktail parties who say, "Oh, you are Dr. Serjeant! You are the chap who never has any severe cases of sickle cell anemia." This shows how badly information can be misread.

I think a point that should be made here is that when you are dealing with an essentially cross-sectional study, an apparent amelioration of clinical course could appear from just selective mortality of severe cases, so that as you get into a group over the age of 30 years, only

the ones that have been mild all along have survived. I want to make it quite clear that this amelioration is not a spurious observation. In fact, these observations are the result of, to some extent, longitudinal studies within the individual patients; retrospective studies, in a sense, in that the patients themselves were in and out of hospitals as children and during adolescence. These patients say that as they got older, their pains became much less severe and much more mild.

I would also like to add something to what Dr. Bowman said about the effect of socio-economic status on the severity of sickle cell disease. Even in non-malarious areas, such as Jamaica, this relationship is clearly apparent between patients who live downtown, patients living in relatively poor parts of Kingston, and middle-class patients living out in the suburbs, despite identical degrees of hematological involvement. Their clinical courses are frequently markedly different. And I think this is difficult to explain.

It is obviously a whole mixture of public health measures, better nutrition, better immunization, easier access to physicians should things go wrong -- a whole host of things.

But the message is that as the whole population over the world moves into better socioeconomic conditions, there will be a tendency for amelioration of the condition.

QUESTION: I just want to respond to the question about the difference between children and adult sickle cell patients, and I think the answer is we do not know. But I think one of the major differences we notice between treating children and adults is the difference in infections. Most of us feel that crises in sickle cell disease are, most of the time, related to infections. Konotey-Ahulu makes that point very strongly. Anybody who takes care of both children and adults notices almost immediately that children have more infections between the age of zero and 10, and sometimes higher, than adults.

DR. SULLIVAN: I have just one other question for Dr. Serjeant. Your mortality rates were highest for children with sickle beta-thalassemia. I do not know whether I missed the point. That was surprising.

DR. SERJEANT: Those rates are meaningless at this point. There were only two deaths.

DR. MAJERUS: I have greatly enjoyed chairing this session on international perspectives in sickle cell anemia and I want to extend my thanks to Drs. Serjeant and Bowman for a most informative presentation. Thank you.

grand rounds: adult case

PRESENTATION OF THE ADULT CASE

David Satcher, M.D.

A 52-year-old Black male was referred to a local medical center on September 8, 1975, for evaluation of sickle cell anemia. He was initially diagnosed as having sickle cell anemia at eight years of age, when he was hospitalized with symptoms suggestive of a painful crisis. The diagnosis of sickle cell anemia was made on the basis of history, clinical findings, and a sickle cell metabisulfite preparation.

Past History

The patient had a slow growth pattern, frequent painful episodes, and associated jaundice during early childhood. Since his initial hospitalization, he has had an average of 12 painful episodes a year, described as mild to severe and usually requiring analgesia, and has been hospitalized on an average of once very two to three years. Pain tends to occur most commonly in the extremities, shoulders, back, abdomen and chest. He was first transfused in 1956, and has been transfused approximately once every other year since that time. His most recent transfusion prior to this admission occurred in January 1975, when he received a total of five units of packed red cells during a hospitalization for bronchitis and influenza.

Painful episodes in the past have been primarily precipitated by over-exertion, sudden changes in the weather (temperature), or alcohol ingestion.

In 1973, he retired from his job as a laborer because of severe, recurring, painful episodes. He has had frequent bouts of pneumonia and notable liver enlargement for more than ten years. He has had ulcers of both ankles in the past and a resection of a left leg ulcer in 1971. There are no ulcers present at this time.

As a youngster, he had several bouts of priapism. He has not been married or fathered any children. Although he did develop sparse pubic hair in his early teens, he has never had axillary or facial hair.

In 1954, he had uneventful surgery for hemorrhoids and suffered rib fractures in an automobile accident the same year. At the present time, he states that he is not a drinker; however, prior to ten years ago his alcohol intake was very heavy. He is being treated for gouty arthritis, which he has had for over five years. Three weeks prior to admission, he had several black stools and an occasional stool with bright red blood. There were no other symptoms and the stools returned to normal within a week.

At the time of admission, the patient's medications included digoxin, benemid, and colchicine.

Family History

He has two brothers with sickle cell trait, and two brothers and a sister with no sickle hemoglobin.

Two other brothers died at a young age, one as the result of an auto accident and the other from pneumonia. The presence of sickle hemoglobin in either of these siblings is not known by the patient.

Physical Examination

Slightly thin male with a protruding abdomen and in no acute distress; blood pressure, 148/76 (right arm); pulse, 72; respiration, 14; temperature, 98.6°; weight, 154.9 lbs.; height, 5'4".

Skin, clear; sclerae, slightly icteric; a positive conjunctival sign was observed biomicroscopically. Best corrected vision was 20-30 in each eye. Optic disc appeared normal. No significant retinal changes were seen by ophthalmoscopy except for a few chorioretinal scars; lungs, clear; heart, point of maximal impulse (PMI) in the sixth left intercostal space 2 cm lateral to the midclavicular line. There was no left ventricular or right ventricular heave. There was a grade II/IV systolic ejection murmur best heard along the left sternal border radiating toward the apex and the base. Abdomen was slightly protuberant without a fluid wave. There was no tenderness. The liver was firm (9 cm below the right costal

margin) extending across the midline and markedly enlarged into the left upper quadrant. Testicles were small; penis unremarkable; pubic hair present (male distribution), but no axillary or facial hair present.

Laboratory Data and Findings

LABORATORY DATA-ADULT

Test	Patient Result
Uric Acid	13 mg%
Calcium	4.15 mEq/liter
Phosphorous	4.9 mg%
Alkaline Phosphatase	126 units/liter (international units)
Total Bilirubin	8.3 mg%
Direct Bilirubin	3.6 mg%
SGOT	101 units per liter
SGPT	3 units per liter
Total Serum Protein	6.2 g%
LDH	1100 U/liter (international units)
Creatinine	1.2 mg%
BUN	17 mg%
Na	136 mEq/liter
K	6.4 mEq/liter
Cl	105 mEq/liter
CO_2	20 mEq/liter
P_{50}	48 mm Hg
Serum Fe	167 mg/100 ml
Total Fe Binding Capacity	186 mg/100 ml
Unsaturated Fe Binding Capacity	19 mg/100 ml
% Saturation	89%

HEMATOLOGY LABORATORY DATA-ADULT CASE

Hemoglobin	7.1 g%
Hematocrit	21.4 vols/%
Red Cell Count	2.0 million/cu. mm
Reticulocyte Count	18.2%
Sedimentation Rate	36 mm/hr.
Platelets	328,000/cu. mm
White Blood Cells	21,500/cu. mm
Differential--polys	75%
Band	1%
Lymphs	16%
Mono	8%

Hb Electrophoresis + SS
Hb F - 0.87%
ISC's - 22.9%
2,3-DPG---------1.04 micromoles/micromole of Hb Tetramer.

The chest x-ray showed moderate cardiac enlargement with increased prominence of the pulmonary vasculature. The electrocardiogram was that of normal sinus rhythm with evidence of left ventricular hypertrophy.

Clinical Course

On September 10, 1975, sigmoidoscopy to 25 cm revealed no abnormalities with the exception of nonbleeding hemorrhoids. Liver and spleen scans (^{99}Tc) revealed an unusually enlarged liver with the left lobe extending far across the midline and into the left upper quadrant. The spleen did not visualize. These findings were corroborated by echo studies. Intravenous cholangiogram revealed a normal common duct, visualization of the gallbladder with no definite filling defects.

The initial stool specimen was slightly positive for blood; however, subsequent specimens were negative. Later the stools were positive for occult blood. The barium swallow revealed reduced esophageal motility and a small hernia. Upper gastrointestinal series, barium enema and intravenous urograms were unremarkable. On September 24, the patient complained of pain in the chest, back and abdomen. He was subsequently given demerol and valium. About four hours later he vomited approximately 600 ml of guaiac positive material.

The hematocrit was 20.4 percent. A nasogastric tube was inserted with subsequent drainage of appoximately 750 ml of guaiac positive material. Vital signs remained stable through the vomiting and lavage. The hematocrit was maintained between 30 percent and 35 percent with transfused packed red cells.

A review of the barium swallow raised suspicion of varices in the distal third of the esophagus. Gastrointestinal endoscopy was performed which revealed the presence of four thrombotic varices present at approximately five to eight cm proximal to the esophagogastric sphincter. There was no evidence of fresh hemorrhage. The varices were raised and bulging into the lumen of the esophagus. No gastric varices were noted.

The patient was treated conservatively with continuous ice saline lavages through a nasogastric tube and transfusions of packed red cells. On this regimen, the patient exhibited no further

vomiting and gastric contents cleared of guaiac positive material. Blood pressure and hematocrit remained stabilized. During the gastroscopy procedure, the patient aspirated gastric material and developed an aspiration pneumonia. The patient was treated with antibiotics with no difficulties.

Because of the physical evidence of hypogonadism, endocrine studies were done with the following findings:

- Skull films, sellar tomograms and an EMI scan documented the presence of a pituitary tumor invading the sella turcica and sphenoid sinus to the sphenoid floor.
- Visual fields and an electroencephalogram were normal as was chromosome testing including Giemsa banding.
- Adrenocorticotropic hormone stimulation studies were suggestive of secondary adrenal cortical insufficiency.
- Follicle-stimulating hormone studies were suggestive of hypogonadotrophic hypogonadism.
- Growth hormone studies were interpreted as normal.
- Baseline thyroid function showed a borderline T3 of 47 and 78; T4 of 4.8 and 5.2, and free T4 1.5; thyroid-stimulating hormone was 3.2.

Of great interest was the markedly elevated prolactin values in the 600-700 range, unchanged by thyrotropin-releasing hormone stimulation.

The above findings indicate that this patient has 1) sickle cell anemia; 2) marked hepatomegaly; 3) upper gastrointestinal hemorrhage; and 4) a pituitary tumor.

The patient was subsequently discharged within three weeks to be followed by his referring physician.

THE INTERNIST'S PERSPECTIVE

Jeanne Smith, M.D.

To intelligently discuss this 54-year-old gentleman with homozygous sickle cell disease, it is essential for us first to sort out the symptoms in his complex clinical picture that are related to sickle cell disease.

Sickle cell disease can involve any organ system, and the manifestations can therefore be protean. It is also true that the individual with sickle cell disease is subject to all of the environmental, infectious, iatrogenic, autoimmune, or other acquired or inherited disorders that affect individuals without sickle cell disease.

During the pediatric grand rounds session, Dr. Pearson discussed the incidence of overwhelming infections in the infant and young child with sickle cell disease, and gave evidence that this was related to the development of hyposplenism at a time when natural immunity is not yet developed.

The protocol tells us that this patient was eight years of age and in the hospital for treatment of a painful crisis at the time the diagnosis was made. If this patient is 54 years old today, clearly he survived his early childhood without an episode of pneumococcal sepsis or other devastating infection. In the late 20's or 30's, when this patient was born, there were no antibiotics available to treat these infections.

Similarly, he was fortunate enough not to have an episode of splenic sequestration -- a complication requiring immediate blood transfusions. Before the late 40's such transfusions were not available.

So our 54-year-old patient survived the hazards of early childhood, tolerated the occurrence of multiple painful crises and priapism during adolescence, and became an adult. As a young adult, he had several episodes of pneumonia. In the older child and the adult, the sequelae of infection are somewhat different. Intravascular sickling provides a setting for tissue necrosis and subsequent infection. Recurrent infection may lead to chronic bronchitis and ensuing pulmonary fibrosis, and in some patients, pulmonary insufficiency.

This patient, interestingly enough, had anterior tibial ulcers which required skin grafts. Leg ulcers occur in a setting of tissue necrosis secondary to minor and often unnoticed trauma to the area around the ankles and the shins. And while anterior tibial ulcers are not common in this country, as Dr. Serjeant well knows, they are frequent in Jamaica. The observation that leg ulcers are infrequent until mid or late adolescence is one that is yet to really be explained.

It is of interest to note that this patient who was described as slow to mature, who was significantly underdeveloped and the recipient of frequent painful crises, episodes of pneumonia, and several hospitalizations was able to work for many years as a laborer despite all of this.

In contrast to Dr. Serjeant's observation that the manifestations of the disease may ameliorate with age, this patient's symptomatology apparently worsened. Three years before this admission his crises became so severe and frequent that he was forced to stop working. One could speculate that an intervening disease was responsible for this increased frequency of crises or, alternatively, that the gradual insidious deterioration that can occur as a result of liver disease made him less able to tolerate his frequent crises.

Whatever the reason for his worsened condition, one of the prime questions concerning his current admission is, What is the etiology of his liver disease? He has had hepatomegaly for a period of ten years, with a history of alcoholism prior to this period. The patient denies any drinking during the past ten years. He has a disorder which is known to be associated with some degree of hepatic disease. And he also has had several other episodes or occurrences in his life which could result in hepatic disease.

To begin with his sickle cell disease, sickle cell hepatopathy has been often described,

but in reviewing the literature one can question whether it really represents a distinct entity. Literature describes the occurrence of sickling within the liver, with hepatic cell damage, and it has been postulated that sickle cell hepatopathy may eventually be a cause of sclerosis and hepatic failure.

It is hard to sort these occurrences out from all the other things that can happen to a patient with sickle cell disease. Not infrequently individuals with sickle cell disease are transfused. Transfusion may lead to viral hepatitis; viral hapatitis may lead to a post-necrotic cirrhosis, which in itself could be the cause of the disorder.

Similarly, patients with sickle cell disease are frequently subject to cholelithiasis. This does not happen to be a problem in this particular patient because his oral cholecystogram and his IV cholangiogram are both within normal limits. But in the setting of cholelithiasis, one may very well see obstruction with the development of biliary cirrhosis.

In addition to the consequences of viral hepatitis as a result of transfusion, multiple transfusions can eventually lead to the development of significant hemosiderosis. This patient has both a high serum iron and a high iron-binding capacity, but if one attempts to estimate the number of transfusions he has received during his life, the number is not so great as to suggest that hemosiderosis would be a predominant cause of his liver disease.

This leaves us with his history of alcoholism as possibly one of the precipitating factors of his liver disease. The patient with sickle cell disease is certainly subject to any disorder which may affect any other individual. The laboratory values are suggestive of hepatic dysfuntion and intrahepatic obstruction, as evidenced by an elevated alkaline phosphatase, hyperbilirubinemia, particularly the direct component, and the elevated SGOT (serum glutamic-oxaloacetic transaminase) -- all consistent with Laennec's cirrhosis. One can then explain his upper gastrointestinal bleeding on the basis of varices.

I would say, very simply, that this gentleman has probably done very well as far as his sickle cell disease is concerned. He has not developed a number of the other complications which we have mentioned along the course of this conference, for example, the development of bone disease, or the development, as Dr. Rabb will discuss later, of ophthalmologic disease. But he has developed one disorder which is unrelated to his sickle cell disease, cirrhosis, and as Dr. Penny will discuss later, he probably has another disorder.

THE HEMATOLOGIST'S PERSPECTIVE

John Bertles, M.D.

I plan to move through the case report and comment as I go. Let me start with the initial identification of the patient's hemoglobin disease by a metabisulfite preparation. I hope that all of us now know that doing a "sickle prep" does not provide enough of a basis to make a diagnosis. Even hemoglobin electrophoresis at an alkaline pH is not sufficient to make a diagnosis of SS because, for example, hemoglobin D runs on the electrophoretogram at the S position. To confirm a diagnosis of SS, I prefer to do both solubility testing and electrophoresis at an acid pH in agar gel. In fact, I do not believe the patient we are discussing has been clearly diagnosed, but let us assume he is SS.

It is interesting to note, a little further into the case report, that the patient had quite a few transfusions. You will notice that when he came in his hemoglobin was seven. He probably had been bleeding. I do not know what his resting hemoglobin during intermission would be. I suspect it was probably a bit higher than seven. I suspect these various transfusions he received may not have been necessary. It has been my experience, and the experience of a number of other observers, that in adulthood it is rather unusual to have to transfuse an SS patient unless, of course, a bleeding episode occurs or chronic organ damage exists, for example, in the liver or kidney. This man certainly has a lot of liver problems.

It must be noted of course that SS patients may develop marrow hypoplasia in acute illnesses. In fact, I note that in January 1975, the patient received a total of five units of packed cells. Hence, one might suspect that he might have become hypoplastic. That is, if one had looked at his marrow, one would have seen that he was not making red cells. This is something that house officers very frequently overlook. Well-educated house officers are aware that it is rare to find a so-called hyperhemolytic crisis. But house officers often do neglect the fact that individuals with SS and other chronic hemolytic states can suddenly turn off their bone marrows and stop making red cells. It is very possible that it was necessary to give this patient these five units for that reason.

Now I'll address the comment about "sudden changes in the weather." This relationship of weather conditions to symptomatology is striking; a cause and effect relationship can occur whether the weather is getting warm or whether it is getting cold. We can expect patients' telephone calls saying, "I hurt, I am in trouble; I have just gone sour." And it does not make any difference which way the thermometer is going. It is the change in the weather that affects symptomatology. Something happens that tips over the balance in a hematologically precariously positioned SS patient to give him more trouble. I think someday the reason for this weather effect is going to come out.

The effect of alcohol ingestion on sickle cell patients is interesting. A number of my patients say that drinking causes them to have pain crises. One possible reason for this is the diuresis that is attendant upon drinking. But some patients say, "I feel pain in my back the moment I take a drink." That is not diuresis. Increased serum osmolality, that is, the concentration of substances in the blood that might be drawing water out of the red cells was proposed as a possible cause of this problem in SS several years ago, but I do not think that has been resolved. At any rate, to net this out, alcohol ingestion frequently does seem to lead to pain in patients who have SS disease.

Priapism is a most difficult problem; it is both physically and psychologically crippling. Most of these episodes of priapism -- I do not know about this man -- occur at night in my patients, usually about the same time from night to night. They can be relieved by getting up, walking around, and exercising. And then by the time morning light comes, the priapism has frequently gone away. I do not believe administration of estrogens helps, and the resulting gynecomastia is disfiguring. I do not really know of anybody who has developed a successful attack on this problem that has not been invasive or destructive, that is, involving surgery.

Gouty arthritis was mentioned in this patient's report. This man could of course have true gout -- it is always possible -- nevertheless, he has a good reason for experiencing symptoms of gout with this uric acid of 13 as a result of his SS disease. Let me pose a question for later discussion: I have two patients now who are on allopurinol. One presented with a uric acid of 17, and the other presented with 13. Both complained of puffy, nonpainful, nontender hands and feet. I wonder if anyone in the audience has seen this. As the uric acid went down, this complaint disappeared. These are adults -- a strange thing. At any rate, there is a good reason for the uric acid to be elevated, and, of course, that is the accelerated red cell breakdown.

Let us look more closely at the patient's laboratory data. The patient came in with a hemoglobin of seven, a fair range for an SS patient, and even then he had been bleeding. You will note that his reticulocyte count was 18 percent, so he was certainly responding well to this low hemoglobin and hematocrit.

Now this elevated erythrocyte sedimentation rate is anomalous. I just asked Dr. Smith, "What is going on here?" and she said, "What about the AA cells?" Of course the patient had been kept at a hematocrit of about 35 by undoubtedly quite a few units of packed cells. Probably a high proportion of his circulating red cells are AA. He has liver disease, his protein electrophoresis pattern is probably abnormal, and therefore he has a good reason for the elevated sedimentation rate. Remember, in SS disease uncomplicated sedimentation rate is usually low. The cells have difficulty settling in an ESR (erythrocyte sedimentation rate) tube.

The platelet count of 328,000 is normal and does not really deserve much comment, except to note that there is an increased platelet turnover in SS individuals, and frequently an elevated count is observed. Apparently there is an even faster turnover of platelets during pain crisis.

The hemoglobin F was low, and the proportion of irreversibly deformed cells, so-called irreversibly sickled cells (ISC's), was 23 percent. As Dr. Serjeant has shown, the greater the proportion of ISC's in the peripheral blood, the shorter the half-life of the red cells. It must still be determined whether or not high proportions of these deformed cells in the peripheral blood have clinical significance. Nevertheless, they are sickle cells.

One abnormal characteristic of these cells is that their ability to carry oxygen is low; that is, the oxygen saturation curve of these cells, which have a high hemoglobin S content, is shifted to the right. Others have recently determined in kinetic studies that these so-called ISC's sickle faster and are more difficult to reoxygenate than non-ISC's. That is, the fibers of deoxygenated sickle hemoglobin tend to persist in them.

This patient has quite a few ISC's, and this may be responsible for the fact that his P_{50}, that is, the partial pressure at which his blood is half-saturated with oxygen, is shifted considerably to the right.

It was once thought that the shift of the oxygen saturation curve, as I just described in SS disease, was caused by the increased amounts of diphosphoglycerate, known as DPG, in the red cells. DPG does compete with oxygen for hemoglobin, if you want to look at it that way. It helps to dislodge oxygen from hemoglobin where it is needed, in the tissues. However, further studies have revealed that the shift in the curve is probably caused by the relative insolubility of deoxygenated sickle hemoglobin. The higher the MCHC (mean corpuscular hemoglobin concentration), the further the curve is shifted to the right.

I think that pretty much covers what I have to say about the hematological aspects of this patient's disease.

THE OPHTHALMOLOGIST'S PERSPECTIVE*

Maurice F. Rabb, M.D.

The clinical description of the patient's eye findings is brief. It reads, "Sclerae slightly icteric; a positive conjunctival sign was observed biomicroscopically. Best corrected vision was 20/30 in each eye. Optic disk appeared normal. No significant retinal changes were seen by ophthalmoscopy except for a few chorioretinal scars." We will discuss each of these findings in turn.

Scleral icterus refers to a yellow coloration of the sclera from bilirubin. It is accompanied by a similar coloration of the skin. When serum bilirubin concentration exceeds 2 to 3 mg per 100 ml, scleral icterus is seen. The preferential binding of bilirubin by elastic fibers in tissue probably explains the propensity of the sclera to show icterus. At higher serum bilirubin levels, all tissues become icteric.

The patient showed a positive conjunctival sign. Although abnormal vascular patterns had previously been noted by others, in 1961 Paton gave the first good description of dark, red, comma-shaped or corkscrew-shaped isolated vascular segments in the conjunctiva. (See Figure 69.) These commas are most commonly seen in the lower bulbar conjunctiva, especially where it is covered by the lid. They require a slit-lamp or the +40 diopter lens of the direct ophthalmoscope to be seen. Paton felt the conjunctival sign was pathognomonic of sickle hemoglobinopathies with no false positives. Swartz and Jampol, however, subsequently reported one false positive case in an individual with leukemia. The heat of the slit-lamp makes the comma sign less conspicuous while vasoconstrictors (for example, cold phenylephrine drops) make the commas more prominent. It has been suggested that a direct relationship exists between the comma sign and the percentage of irreversibly sickled cells. In this regard it is interesting that the comma sign has been reported as positive in 84 to 96 percent of SS patients, and 15 to 80 percent of sickle cell patients. It can also be seen with S-thal patients.

Figure 69. Dark, red, comma-shaped or corkscrew-shaped isolated vascular segments seen in the lower bulbar conjunctiva through +40 diopter lens of the direct ophthalmoscope.

Next we turn to the optic disk. Potentially, both the sickle cell disease and the sella tumor could have affected the optic nerve heads. We have noted small microvascular occlusions of vessels on the optic nerve head in individuals with SS disease. These tiny occlusions probably represent capillary blockage by sickled erythrocytes and are transient. They do not affect vision. Much more rarely, optic nerve neovascularization can be seen in patients with sickle hemoglobin.

Sella turcica tumors can result in visual field loss and optic atrophy. The most characteristic field change would be a bitemporal hemianopia. The patient did not show these changes, but this is certainly not unusual.

Finally, we turn our attention to the black chorioretinal scars. These scars, often called black sunbursts, are seen most commonly in SS disease but can also be seen in patients with hemoglobin SC and S-thal. (See Figure 70.)

*From the paper "Ocular Manifestations of Homozygous SS Disease" by Maurice F. Rabb, M.D., and Lee M. Jampol, M.D.

The etiology of these sunbursts had been uncertain, but recently Asdourian and associates demonstrated the evolution of black sunbursts from intraretinal hemorrhages. A sudden arteriolar occlusion leads to an intraretinal hemorrhage, which is often salmon colored and called a "salmon patch." If the hemorrhage dissects into the outer retina, it irritates the pigment epithelium of the retina resulting in a black sunburst.

The patient's vision was described as 20/30 in both eyes. It is uncertain from the history what was the cause of this visual loss. Patients with SS hemoglobin can show vascular occlusions in the macula. Acutely these appear as cotton wool spots with an obstructed precapillary arteriole and a nonperfused region of retina. Often the capillary bed becomes reperfused. Microaneurysmal dots, hairpin capillary loops, and enlarged segments of terminal arterioles can be seen.

Figure 70. Black chorioretinal scars or black sunbursts.

The most devastating complication of sickle cell retinopathy is the formation of neovascularization from the retina, the so-called sea fans. (See Figure 71.) These sea fans can lead to vitreous hemorrhages and tractorial or rhegmatogenous retinal detachment. This patient did not demonstrate sea fans. Initially neovascularization was felt to be rare in patients with SS disease compared with SC and S-thal. Condon and Serjeant found it in only 2.6 percent of patients of all ages with SS hemoglobin. Recently, however, the same authors have found that above age 45, neovascularization is not rare in patients with SS hemoglobin. In fact, in patients above age 50, it was noted in 29 percent of cases. In patients of all ages, however, patients with SS hemoglobin have a lower incidence of serious ocular complications than patients with SC and S-thal. This is despite the fact that other systemic manifestations are almost uniformly worse in patients with SS.

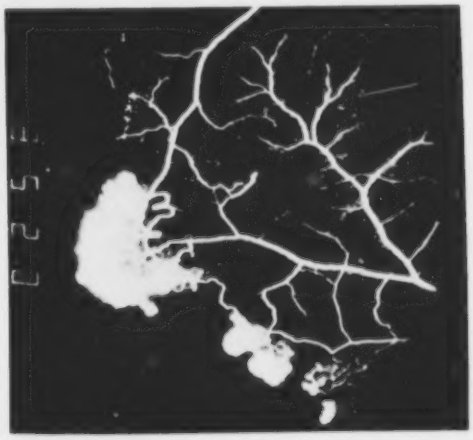


Figure 71. Neovascularization from the retina, the so-called sea fans.

In conclusion, I would like to say that should a patient have hemoglobin SS, SC, or S-thal, he deserves to have a yearly eye examination including careful fundus evaluation. This should be done despite the fact that the patient is often asymptomatic. Many of the eye changes cannot be seen by the internist with a direct ophthalmoscope and thus ophthalmologic consultation is a necessity.

THE ENDOCRINOLOGIST'S PERSPECTIVE

Robert Penny, M.D.

It is my impression that I have been asked to discuss this case because of the subject's apparent impaired sexual development. Sickle cell anemia may be associated with impaired sexual development. Additionally, discussion of the case allows one to point out that even if an individual has a disorder which could be identified as a cause for impaired sexual development, care must be taken to eliminate other possible etiologies. Initially, I will review the physiology relevant to sexual development. Subsequent to this, I will discuss the findings present in the case.

Table 19 lists the pertinent hormones in sexual development. The sex steroids, testosterone and estrogens, are responsible for the physical changes and secondary sex characteristics which constitute sexual development. These steroids are produced and secreted, by and large, by the gonads (testes or ovaries). Production and secretion of the sex steroids by the gonads is maintained by the gonadotrophic hormones of the anterior pituitary, which are themselves regulated by the plasma concentrations of the sex steroids. This relationship of the product (sex steroids) regulating the stimulus for the production of the product (gonadotropic hormones) is termed feedback.

Table 19. Sex Hormones

A.	Steroids
	1. Androgens (testosterone; androstenedione)
	2. Estrogens
B.	Gonadotropins
	1. Luteinizing Hormone (LH)
	2. Follicle Stimulating Hormone (FSH)
C.	Prolactin

Plasma sex steroid concentrations less than physiologic result in increased gonadotropic hormone secretion, and plasma sex steroid concentrations greater than physiologic result in decreased gonadotropic hormone secretion. Absent or deficient gonadotropic hormone secretion causes the gonads to cease to produce and secrete adequate amounts of sex steroids. In contrast, an absence or deficiency of sex steroids results in greatly increased secretion of gonadotropic hormones.

There are two pituitary hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH in combination are responsible for the growth of ovarian follicles and the production and secretion by the follicles of estrogens. LH is responsible for corpus luteum formation and, in combination with FSH, for ovulation. In the male, spermatogenesis is dependent upon the stimulation of testicular tubules by FSH; and testicular Leydig's cells, the producers of testosterone, are under the control of LH. Gonadotropic hormones in the adult female are secreted cyclically in varying amounts, and in the adult male they are secreted in a relatively constant, tonic fashion.

Gonadotropic hormones are secreted at low levels until the onset of puberty. It is postulated that puberty is due to an increase in gonadotropic hormone secretion which occurs as a result of decreased sensitivity of the pituitary and/or the hypothalamus to the levels of circulating sex steroids.

Prolactin is unique among the anterior pituitary hormones in that it is regulated by a hypothalamic inhibiting factor (prolactin inhibiting factor, or PIF).

The only established role for prolactin in human subjects is the initiation and maintenance of lactation in a properly prepared mammary gland. Mechanical stimulation of the female breast, but not the male breast, leads to a massive secretion of prolactin. A number of nonspecific stimuli also result in prolactin secretion, including surgical stress, uremia, and exercise. The physiologic significance of this prolactin secretion is obscure.

Pharmacological agents such as L-dopa (which normally decreases it) and TRH, thyrotropin releasing hormone (which normally increases it) affect prolactin secretion.

Elevated prolactin concentrations have been found in such pathologic conditions as pituitary

tumors, hypothalamic disorders, pituitary stalk section, hypothyroidism, Nelson's syndrome, and ectopic production by malignant tumors.

Sexual hair, pubic and axillary hair, is the result of testosterone action. (See Table 20.) The adult male plasma testosterone concentration is 400 to 1000 ng/100 ml; 95 percent or more of this is contributed by the testes and the remainder by the adrenals, directly or indirectly. The adult female plasma testosterone concentration is 20 to 70 ng/100 ml. Five to 20 percent of this is contributed by the ovaries. The remaining 80 to 95 percent is contributed by the adrenals, directly or indirectly (0 to 30 percent is secreted by the adrenals as testosterone and 50 to 70 percent is derived from androstenedione secreted by the adrenals and converted by the liver and other peripheral tissues to testosterone).

Table 20. Sexual Hair

Sexual hair, pubic and axillary hair, is the result of testosterone action. The source of the testosterone is:
Males: - (400 to 1000 ng/100 ml)
95 percent from the testes
5 percent from adrenals (directly and indirectly)
Females: - (20 to 70 ng/100 ml)
5 to 20 percent from the ovaries
95 to 80 percent from adrenals (directly and indirectly)

Testosterone-gonadotropin feedback regulates testicular secretion of testosterone. Ovarian testosterone secretion and adrenal androgen (testosterone and androstenedione) secretion are not under direct feedback control. Secretion of testosterone by the ovaries is a by-product of estrogen production, estrogen-gonadotropin feedback being the regulating influence; and adrenal secretion of androgen may be viewed as a by-product of cortisol production, cortisol-ACTH feedback being the regulating influence.

The significance of the above information is that in the absence of all sexual hair one has to consider the possibility of both adrenal and gonadal deficiency being present. Hypopituitarism is the usual cause of such an occurrence.

Shown in Table 21 is a classification of the etiologies of impaired sexual development. Delayed adolescence represents a deviation from the mean age at which a given state of sexual maturation is usually achieved. The term by definition means that normal sexual development is ultimately attained. Transient gonadal impairment is associated with gonadotropin concentrations which are elevated for state of sexual development; and delay in change of hypothalamic setpoint is associated with gonadotropin concentrations low for age but appropriate for state of sexual development.

Hypogonadism means that a male does not have testes which are at least 2 cm by age 14 or a female does not have breast development by age 13 and/or indicates that normal sexual development is never attained and/or maintained. In primary hypogonadism, gonadotropin concentrations are elevated; and in secondary hypogonadism, they are inappropriately low for state of sexual development. Each of these etiologies of impaired sexual development has been reported in subjects with sickle cell anemia. I have listed in Table 22 the factors which should be considered in the evaluation of impaired sexual development.

Table 21. Classification of Etiologies of Impaired Sexual Development

A.	Delayed adolescence
	1. Transient gonadal impairment? (pseudo-delayed adolescence)
	2. Delay in change of hypothalamic setpoint as related to age (true delayed adolescence)
B.	Hypogonadism
	1. Primary (gonadal failure)
	2. Secondary (pituitary and/or hypothalamic failure)

Table 22. Evaluation of Impaired Sexual Development

A.	History: growth, polydypsia and polyuria; familial incidence; sickle cell anemia
B.	Physical examination: height, BP, eunuchoidism, gynecomastia, neurological - visual fields, sense of smell, extent of sexual development (presence or absence of sexual hair and/or breast development and/or palpable uterus and/or testicular size).

C. Laboratory: skull x-rays, bone age x-rays; LH and FSH, prolactin (if elevated), sellar tomograms and/or EMI scan); karyotype.

Findings pertinent to the patient are given in Table 23. The patient's slow growth during childhood is consistent with the clinical course of his sickle cell anemia. Sickle cell anemia subjects may show growth impairment during childhood and adolescence. His normal adult height suggests that his growth was not totally impaired, a finding which is true, by and large, for most sickle cell subjects. Development of pubic hair during adolescence and the presence of a normal adult penis and testicular size suggest that adequate Leydig cell and gonadotropin function were at one time present. The absence of axillary and/or facial hair associated with otherwise normal sexual development does occur, but it is rare.

Table 23. Pertinent Findings of a 52-Year-Old Male with Sickle Cell Anemia (SS)

A. Historical:
   1. Slow growth pattern during childhood.
   2. Developed pubic hair but not axillary or facial hair in early teens.
   3. Since diagnosis of SS at age 8 years, has had 12 crises per year and hospitalized every one to two years, the last time in January, 1975.

B. Physical Examination:
   1. General: BP 148/76, TPR 36°C-80-18. HT: 175 cm (normal 176.5±10.2 cm), WT: 70.4 kg (normal 75.5± 12.6 kg).
      Span: 190 cm (normal span should exceed ht. by not more than 5 cm).
      Ratio of upper body segment/lower body segment = 83 cm/92 cm = 0.90 (normal 0.97-0.99).
      Normal neurological examination including visual fields.
      Normal sense of smell.
   2. Sexual Development: Testis - right 4.2 x 2.0 cm; left 4.5 x 2.5 cm, penis unremarkable, pubic hair present, no axillary or facial hair present; no gynecomastia.

C. Laboratory:
   1. Anatomical and Miscellaneous: skull films, sellar tomograms and EMI scan document presence of an intra-sellar tumor; normal male karyotype.
   2. Endocrine:
      a. Adrenal Studies: Basal-17-hydroxy corticosteroids - 4.0 mg/24 hrs. (normal 3-9 mg/24 hrs.)
      Response of 17-hydroxy corticosteroids to ACTH stimulation -- increased to 26 mg/24 hrs. (normal - should increase by 5 to 10 times basal)
      Basal-17-ketosteroids -- 4.0 mg/24 hrs. (normal 7-17 mg/24 hrs.)

      b. Gonadotropins and Testosterone: Basal - LH 4.4 mIU/ml (normal 10.9 ± 4.0 mIU/ml), FSH 1.7 mIU/ml (normal 7.4 ± 1.9 mIU/ml; testosterone 38 ng/100 ml (normal 400-1000 ng/100 ml). Response to LRH -- LH increased to 18.3 mIU/ml and FSH to 4.8 mIU/ml (normal should increase by 3 to 10 times basal).

      c. Thyroid Studies: Basal -- Thyroxine 5.2 µg/100 ml (normal 4.0-11.5 µg/100 ml). Free thyroxine 1.5 ng/100 ml (normal 0.8 to 2.4 ng/100 ml). Thyroid stimulating hormone (TSH) 3.0 µU/ml (normal 0-10 µU/ml). Response of TSH to TRH -- TSH increased to 13.0 µU/ml (normal TSH should increase 10-20 µU/ml above basal).

      d. Growth Hormone: Response to L-dopa -- it increased from 1.6 ng/100 ml to 4.0 ng/100 ml (normal should increase 5 to 7 ng or more above basal). Response to insulin-induced hypoglycemia -- it increased from 6 ng/100 ml to 20.6 ng/100 ml (normal should increase 5 to 7 ng or more above basal).

      e. Prolactin: Basal -- 600 to 700 ng/ml (normal 0 to 28 ng/ml). Response to TRH -- no change (normal prolactin concentration should increase).

His body proportions (span 15 cm greater than height and upper/lower ratio of 0.90) are eunuchoid. While eunuchoid body proportions may accompany impaired sexual development, it is also seen in normal Blacks. He did not have gynecomastia. Gynecomastia, eunuchoid body proportions, and impaired sexual development are found in Klinefelter's syndrome.

These individuals have an abnormal karyotype and abnormal testes. Kallmann's syndrome, the inheritance of an abnormal sense of smell associated with gonadotropin deficiency, is unlikely because his sense of smell is normal.

His history of tolerance of an eventful clinical course with regard to his sickle cell anemia is consistent with presence of normal adrenocortical function which is confirmed by his normal 17-hydroxy-corticosteroid studies. Since 17-ketosteroids are products of metabolites derived from the adrenal cortex (the major contributor) and the testes, his low 17-ketosteroid excretion is consistent with impaired testicular function.

The basal FSH of 1.7 mIU/ml is greater than two standard deviations below the mean of normals, and the LH of 4.4 mIU/ml is inappropriately low for a testosterone concentration of 38 ng/100 ml. Luteinizing releasing hormone (LRH) resulted in a subnormal FSH response. In the presence of normal testosterone concentrations, his LH response to LRH would be considered normal. But in the presence of low testosterone concentrations, his LH response is subnormal. Thyroid studies both basal and in response to TRH are normal. A failure of L-dopa to cause an increase in serum growth hormone concentration may occur as a variation of normal. The normal growth hormone response to insulin-induced hypoglycemia suggests the retention of at least one physiologic control of growth hormone release.

This patient's elevated prolactin levels are consistent with the presence of a pituitary and/or hypothalamic tumor. The skull films, sella tomograms, and EMI scan document the presence of an intra-sellar tumor. A high incidence of clinically inapparent prolactin hypersecretion occurs with pituitary tumors. A failure of prolactin to increase in response to TRH, which acts directly on the pituitary cells, would suggest the presence of autonomous secreting lactotrophs. Similarly, a failure of L-dopa, which causes an increase in PIF, to produce a decrease in prolactin would be consistent with the presence of autonomous secreting lactotrophs.

In summary, the clinical findings and laboratory data of this 52-year-old male with sickle cell anemia are compatible with impaired anterior pituitary function, gonadotropin deficiency due to excessive growth of autonomous lactotrophs. Previously, pituitary tumors which showed no clinical evidence of function were classified as chromophobe tumors. But evidence has accumulated that there may not be a separate chromophobe cell type since additional staining techniques and, particularly, immunofluorescent and electron microscopic observations have demonstrated that these may merely represent degranulated cells, corresponding to other identified cell types, particularly somatotrophs and lactotrophs. Surgical removal of the tumor by the transphenoidal route, if possible, should produce a satisfactory result in this patient.

DR. SULLIVAN: I think that this patient has served as a very good case for discussion of a variety of interesting facets, many of them related to sickle cell disease, others not related to sickle cell disease. This patient has certainly given us an opportunity to have a fairly comprehensive and complicated case discussed in some detail. I would like to open the discussion now for questions or comments from members of the audience.

QUESTION: This question is directed to Dr. Penny. Did you find a significant number of homosexuals among the SS patients in your study?

DR. PENNY: No. That is an interesting question. Why do you ask?

QUESTION: I raise the question because you discussed in great detail the distribution of hormones.

DR. PENNY: Right

QUESTION: And the homosexual problem, as I understand it, is a disturbance in the distribution of hormones in the male.

DR. PENNY: No. I can refer you to an article that we published not more than two years ago (J. Clin. Endocrinol. Metab. 39: 796, 1974) in which we measured sex hormone concentrations during a one-month period in a group of homosexual males and in a group of normal males. There was no difference found with regard to sex hormone concentrations between the two groups. Their entire problem, I assure you, is supratentorial.

DR. HARKNESS: Would one of the panelists care to comment about the BUN (blood-urea-nitrogen) in this patient? I believe it was listed as 17 at the time the patient came in. Do we have any other values that someone would make a comment on, for example, the possibility of some renal impairment in this patient?

DR. SMITH: Was the last thing you said you would not anticipate seeing is a normal BUN?

DR. HARKNESS: I would anticipate seeing a BUN very much lower.

DR. SMITH: The patient's creatinine and BUN are pretty consistent with each other. But I think you are quite right. It is hard to explain why the patient had a BUN of 17. We only had the one value to work with. One could postulate a variety of reasons, including some degree of dehydration at the time of admission, to explain why the patient's BUN may have been somewhat elevated despite his liver disease. It is a mild elevation.

DR. SERJEANT: Would the panel care to comment on whether they feel cirrhosis is integrally related with sickle cell disease as a pathology, or whether it is just a side effect of treatment, such as transfusion therapy?

DR. SMITH: I think it is almost impossible to sort out an answer to this question completely. One can say there are many individuals who reach adulthood who do not develop cirrhosis *per se*, if by cirrhosis you mean the development of actual fibrosis and progression of that into portal hypertension, and whatever.

One of the reasons it is impossible to sort this question out is the number of other things that can happen to an individual with sickle cell disease that can have an impact on his liver, for example, the effect of repeated episodes of cholelithiasis, cholecystitis, and perhaps ascending cholangitis, with biliary cirrhosis developing secondary to that, not to mention, as we indicated before, the complications of transfusion, hemosiderosis, and hepatitis. Here you have an individual who also has a history of alcoholism which alone can produce cirrhosis.

DR. MURRAY: It has been stated or there have been anecdotal reports of an association between sickle cell trait and cardiomyopathy associated with heavy drinking. Can any of the clinicians comment on the relationship between alcoholism or heavy drinking in patients with sickle cell anemia and the occurrence of cardiomegaly or cardiomyopathy?

DR. SULLIVAN: In your question you said "and sickle cell anemia?" Did you mean that?

DR. MURRAY: For example, here is a patient who was a heavy drinker. There was cardiomegaly. Was there any evidence this might

have been associated with cardiomyopathy? Is there any experience? The reports on sickle cell trait are anecdotal.

DR. SULLIVAN: Right.

DR. MURRAY: One would expect if the sickle cell trait is associated at all with cardiomyopathy, a patient with sickle cell anemia would show some evidence of this. My feeling is that the association is spurious. Is there anything in sickle cell anemia or sickle cell disease to suggest such an association?

DR. SATCHER: I do not know of anything. I have not seen any reports. I do not know if we have had that much experience with alcoholism and sickle cell disease yet to be sure.

This patient is sort of confusing in that he was on digoxin, and it is not clear to me why this patient was on digoxin, although it may also relate to the liver problem. But there is no history of heart failure in this patient, no history of dyspnea on exertion, shortness of breath, PND, orthopnea, and yet he is on digoxin. And yet we know that cardiomegaly in sickle cell disease, as Dr. Friedman said yesterday, is somewhat compensatory in that the increased shortening distance compensates for the fact the patient is anemic and has peripherovascular dilatation.

The experience with any high output failure is that digoxin does not have a dramatic effect on it. You really have to treat the basic cause, whether you are dealing with thyrotoxicosis or acidosis or anemia. If a patient comes in with high output failure, the main therapy, of course, is going to be dealing with the basic cause.

And to Dr. Bertles' indication for transfusion, I would add congestive heart failure in a patient with sickle cell disease whose hematocrit or hemoglobin drops very low I think that is an indication for treatment with a transfusion of packed cells.

This patient has no history of congestive heart failure. We have the enlarged heart, which is consistent with sickle cell disease in a 54-year-old patient, and even in younger patients. We have the murmur which sounds like the flow murmur you hear with an anemic state.

But the other question, however, is whether or not as patients with sickle cell disease get older, we are going to see more renal failure and more congestive heart failure. And that is what everyone says. But in our experience, the patients we have seen with renal failure have not been those in their 40's and 50's. They have been certain select patients in their 20's, from 25 to 30, who come in with renal failure and who seem to have more difficulty with congestive heart failure. So I do not really know the answer to that or to the question you raised. There are no reports on it.

DR. MURRAY: Can any of the other clinicians respond to the question, or is there just no information? Does anybody else have any experience in this area, particularly with sudden death? I think the initial reports were indications of cardiomyopathy, sudden death, and heavy drinking, all associated with the sickle cell trait. Does anybody have any isolated cases of this type of association in his experience?

DR. SMITH: I have no experience, but I agree that this may just be an example of the strategy for getting a case report into the literature by hanging sickle cell trait onto whatever happens to a patient. Sudden death, probably due to arrhythmia as a complication of alcoholic cardiomyopathy, is certainly a well-known phenomenon in an individual with no sickle cell trait whatsoever, so I do not know that we can make much of it. Unfortunately, I have not read those references.

QUESTION: I wonder if someone would comment on the sickle C patient going above certain altitudes and losing his vision. We come from the Pike's Peak region where this is being discussed. They are going back and reviewing all of their SC patients, doing ophthalmological exams, and so forth.

DR. SULLIVAN: Is it permanent or transient loss of vision?

QUESTION: Permanent, as I remember when we visited the center there. They had one patient who had gone above a certain altitude and had lost her vision, and as far as I know it is permanent. This incident occurred in the Pike's Peak area which is 14,000 feet above sea level.

DR. RABB: I am very glad you asked that question because I think that anyone who has eye problems at a high altitude should have an eye examination. There is a particular entity called high altitude retinopathy, which is seen in individuals with any type of hemoglobin, including individuals with AA hemoglobin.

There are two recent reports in the American Journal of Ophthalmology on retinal hemorrhages in climbers. These hemorrhages may cause transient loss of vision. The hemorrhages were documented by fundus photography. In addition, isolated reports of central retinal artery occlusion occurring at high altitudes in individuals with sickle hemoglobin have appeared. Do you know what type of hemoglobin the patient had?

QUESTION: SC, I believe. We saw one patient come into the research center and, as I remember, she was an SC, and they were talking about going back and reviewing their other SC patients.

DR. RABB: We frequently see individuals who suddenly lose their vision with SC at sea level. The association with high altitude would be difficult to prove because a common manifestation of sickle cell disease is occlusive retinal vascular disease, no matter what the elevation, no matter what the occupation, no matter what the age, no matter what the hematologic factors. The presence of hemoglobin SC alone is enough to cause visual loss, even without the altitude. It would, however, be of interest to see if visual loss is more common at high altitudes in these patients.

DR. SULLIVAN: I would like to make some comments, and then direct a question to Dr. Bertles. This patient's MCV (mean corpuscular volume) was actually large. He had macrocytic cells, I think an MCV of 107. The question is whether this may be due to simply the high percentage of reticulocytes, due to this patient's hemolysis, or due to his folate deficiency related to his alcoholism. I think something like 80 to 85 percent of alcoholics with cirrhosis have folate deficiency, as defined by low serum folate levels. Dr. Bertles might want to comment on that. The other question I have is, Could this man's serum iron level be related to the possibility of having sickle beta-thalassemia disease, or does one see different serum iron levels in these patients, as opposed to homozygous S disease patients?

DR. BERTLES: Dr. Sullivan picked up something I missed completely. This high MCV certainly could be the result of impending folic acid deficiency. This is a clinical point that deserves emphasis. It should be remembered that individuals with SS, SC, S-thal, and other severe chronic hemolytic anemias can slip into folic acid deficiency. One always has to be alert to this. Certainly young red cells have a high MCV. But I think the most important teaching point to be made in the circumstances is that this patient could possibly be slipping into folic acid deficiency.

As far as the serum iron level in this particular individual is concerned, I think the case is so confused I could not make a rational comment on this question.

DR. SULLIVAN: I also would like to comment on an observation you reported, and perhaps ask you another question. We saw an adult patient at the Boston City Hospital about two years ago who developed puffy hands and feet, interestingly, which were pruritic, but not red, as in the children with hand-foot syndrome. This disappeared in about four days. I am not sure if this is the same thing you observed in the patient.

DR. BERTLES: Was the uric acid high?

DR. SULLIVAN: I do not recall that we got a uric acid, or at least I do not remember that. We were not aware of the uric acid.

DR. BERTLES: Did you have any explanation at all for the puffy hands and feet?

DR. SULLIVAN: No, we spoke with a number of hematologists in the area, and no one had ever seen anything like it. It looked almost like an adult version of hand-foot syndrome.

DR. BERTLES: Exactly. Has anybody in the audience seen this in SS patients or SC or S-thals?

QUESTION: We had a 37-year-old SS patient who presented with swollen hands, but not feet, but both knees were swollen. He had bilateral knee effusions. We isolated uric acid crystals

from the knee joint, and his serum uric acid was 17. He was treated with allopurinol and recovered. He took himself off the drug and presented again with swollen hands. I had slides of both of his hands, but I really had no explanation.

While he was on allopurinol, his hemoglobin fell drastically. I was wondering whether anybody else has seen a significant drop in hemoglobin in a patient on allopurinol. This patient was admitted two or three times with swollen hands and knee effusions.

DR. SULLIVAN: Where are you from? What clinic is this?

QUESTION: Michael Reese, Chicago.

DR. BERTLES: I think maybe we have all just learned something. This is very interesting. In the patients we had, I did not see a drop in hemoglobin with allopurinol. But I think it is very interesting about the puffy hands. Nontender?

QUESTION: Nontender.

DR. SERJEANT: One of the characteristic things about the hand-foot syndrome generally is the very tight age distribution. It is unusual, certainly before three months, and relatively unusual after five years.

I have only seen one case that was an exception to this, and this was a girl of 13 with SC disease. She had had the hand-foot syndrome in childhood, and had one of those rather unusual complications where you get infarction of the central part of the epiphysis of the involved metacarpal, with a permanent shortening and deformity of the metacarpal. As a result she had a short finger with knuckles much shorter than one would expect. She developed a red, painful, tender swelling over this, and I thought this was really something very unusual.

The swelling then suppurated and drained off. And as far as we know, it was a subcutaneous abscess overlying the deformed bone. Our first reaction, of course, was that she had an osteomyelitis of this deformed bone. But, in fact, the bone did not change at all. She developed no radiological abnormalities besides the ones she already had, and the whole thing was over quite quickly.

Coming back to the swelling of the fingers which, of course, is not easily confused with the hand-foot syndrome, I am referring to the swelling of the actual joints. It might be an interesting starting point for the work on SLE (systemic lupus erythematosus) in sickle cell anemia. There are a number of case reports in the literature concerning the association between SLE and sickle cell anemia, to which two reports were added only two or three months ago. We had, in fact, another three cases, so we now have five.

SLE is certainly common in the Black population in Jamaica. Whether this is a real association or not we do not know. The immunologists are very excited because I gather there is some evidence that SLE develops following a defect in the immune pathway, and, of course, this is established in SS disease.

DR. LUBIN: I wanted to make a comment to confirm what Dr. Rabb had to say. Several years ago, because of the work that Dr. Rabb had done, we began having all the children who are involved in our sickle cell program in Children's Hospital in Oakland have yearly ophthalmological examinations to look for early retinal changes.

The question I wanted to ask was, What is the youngest SC patient you have seen with early retinal changes? This past week, a 13-year-old child, who was asymptomatic, was diagnosed as having early retinal changes, hopefully at a point where something can be done before the changes progress. That was the earliest age we had seen. Perhaps you have had experience with younger children?

DR. RABB: Five years of age, proliferative retinopathy in SC.

DR. LUBIN: The other question I wanted to comment on was the iron situation in sickle cell disease. I think all too often we are fooled by the concept that with the process of transfusion, the patients are not going to become iron-deficient. And as many of you may know, in the work that was done at the Rockefeller Institute as part of their cyanate studies, they did bone marrow aspirations and found a large number of patients had no stainable iron at all in their marrow. We have MCV's on all our patients and we get suspicious of sickle beta-thalassemia

when our MCV's are low. A large percentage of our pediatric population, 20 percent of them, have iron deficiency as well.

These are certainly not patients who are transfused every week or every month. But iron deficiency is also a disorder that is seen in all pediatric patients, whether they have sickle cell disease or not, and we should be alert to that. I suspect in adults we might see similar types of things. I am not sure of that.

DR. HARKNESS: On that same point, following those observations by the Rockefeller people, we did bone marrow aspirations. When we terminated our study, 14 out of 17 patients had no scannable iron in their marrow, although we had taken large samples of blood from these patients over a two-year period. So I wondered if the results had not been iatrogenic.

I just had a call from a pathologist in Chicago where they have recently gotten together an autopsy series of 14 patients with homozygous S. I do not know their history of transfusion, but the patients have no scannable iron in their marrow, although they have extensive deposits of iron over the rest of their body.

DR. LUBIN: I am commenting since you were asking the audience if they have had similar clinical experiences.

We had an experience with an 18-year-old girl who had gallbladder disease requiring cholecystectomy. Three weeks after her surgery -- she had been transfused prior to the surgery -- she became acutely anemic and was admitted to the hospital. Prior to the surgery she did not have a palpable spleen and had not had one actually palpable for a good 12 years. Her spleen became grossly enlarged, approximately ten centimeters along the left sternal border.

We did a technetium sulfur colloid scan, and there was absolutely no uptake in the sulfur colloid. When we labeled the red cells with technetium her spleen lit up like a lightbulb, demonstrating perhaps different functions obviously of the spleen. But this was a situation where we thought the spleen was completely infarcted, and yet it enlarged acutely and sequestered her peripheral red cells.

Has anybody had a sequestration crisis like that, or a situation where a patient who previously did not have a palpable spleen developed an acutely enlarged spleen, resulting in anemia?

DR. SULLIVAN: Did the spleen then subsequently recede?

DR. LUBIN: She had to have a splenectomy. We transfused her and it kept dropping down. We took out the spleen, and it was grossly enlarged, fibrotic. There were infarcted areas, but it was obviously there.

DR. SMITH: Two years ago we lost a 52-year-old lady with sickle beta-thalassemia secondary to splenic sequestration associated with DIC.

DR. SULLIVAN: That is really not quite the same, though.

DR. SMITH: No, it is not exactly the same, but in reviewing the literature I found one other episode of splenic sequestration in an adult, also a sickle-thal. It is obviously very unusual in either disorder.

DR. SERJEANT: While we are trading anecdotal cases, maybe I can add a little to this. We saw exactly the same case -- not in acute splenic sequestration -- but a case involving a girl who had been followed almost from birth, whose spleen had become impalpable from the age of about five. We had not felt it right through her adolescence. At 20 she came in pregnant with a number of pulmonary problems, then went into congestive cardiac failure. And her spleen, in fact, did enlarge at that time. It was not a life-threatening situation, but it had been assumed that the spleen was irreversibly infarcted. And, of course, even if the spleen is no longer palpable, that does not mean it is not just sitting there under the ribs, still capable of becoming enlarged.

QUESTION: To get back to the question of iron deficiency, we also had occasion to observe two individuals with SS in the adult stage who developed iron deficiency anemia. Interestingly enough, during the period of iron deficiency, their red cell count increased while their hemoglobin and hematocrit dropped. With the administration of iron, the red cell count dropped and hemoglobin and hematocrit increased, which was very interesting.

I was wondering, since there is a great deal of attention paid at the present time to ferritin levels, if any of the panel has had any experience with ferritin levels as a reflection of the iron storage situation in sickle cell anemia.

DR. LUBIN: We are beginning to collect information concerning this right now. In fact, the information seems to be correlating with the iron deficiency picture.

DR. SERJEANT: I wonder if I could ask Dr. Rabb a question. He seemed to be at a loss to explain the increased prevalence of retinitis proliferans in SC disease over that of SS. Is that correct?

DR. RABB: No, what I was discussing was the higher incidence of black sunbursts in SS, although apparently we see more salmon patches in SC. This I cannot explain, because we feel that the salmon patch can be the precursor of the black sunburst.

DR. SERJEANT: Would you care to speculate on why SC disease has more retinitis proliferans?

DR. RABB: This may be a manifestation of a higher whole blood viscosity in patients with SC disease. These patients, in general, have higher hematocrits than SS disease. We are attempting to relate whole blood viscosity with the degree of proliferative retinopathy.

DR. SERJEANT: I think this is a very interesting point because certainly among our SC population, if you look at the distribution of steady-state hemoglobin levels, it runs anywhere between 8 and 16 grams, with a fairly normal distribution, and a mean of 12.

If you look at the distribution of your retinitis proliferans patients throughout that hemoglobin distribution, in the Jamaican experience, they are almost entirely in the group of 12 grams and above. And if you are at 14 grams and above, you have about a 95 percent chance of developing retinitis proliferans. On the basis of that data do you feel one should approach the problem by actually lowering the hematocrit?

DR. RABB: This has been brought up before. We really do not know. A second question is whether transfusions in patients with SS increase the chance for retinitis proliferans.

DR. SMITH: We argued that one the other day, and my answer to that was there is a fair amount of evidence that by transfusing with AA blood, one may actually reduce viscosity. I think clinically the reports of reversal of cerebral pathology after transfusion could be interpreted as support for this idea.

In answer to your question -- Should you phlebotomize an SC who is having retinitis? -- I would suggest that perhaps it should be tried.

It would also be interesting to look at one other thing, and that is the incidence of retinitis in iron-deficient patients with sickle cell disease, because it seems to me, there again, your retinopathy might be somewhat less.

QUESTION: I think Dr. Serjeant mentioned the possibility of reducing the red cell count in SC patients. I think it is also noted that SC patients have more incidents of aseptic necrosis of the femoral heads. They think this is directly related to the increase in viscosity, sludging, and occlusion. Sickle cell patients also have increased numbers of renal problems.

I think in Chicago they did try doing phlebotomies on the sickle cell patients who had very high hemoglobins and hematocrits over the 14 to see whether it was reversible. I think the number of patients used was too small to come to this conclusion.

In our clinic we have seen the patients with SC hemoglobins, with hemoglobins 15 and over, who I can send to the eye clinic, and they will call me back and tell me they do have those changes. Also, if you did an X-ray of the pelvis, you would find it almost correlated with the increased incidence of the aseptic necrosis.

DR. SULLIVAN: I would summarize by saying I think this patient has provided an excellent forum for discussion of the various ramifications of sickle cell disease. I think it is difficult to provide an overview that is really comprehensive because of the various facets of this man's problem, which were very complicated. Many of them related to his sickle disease, many other probably did not, such as his liver disease, possibly his varices, and so on. Dr. Penny does not feel the patient's pituitary tumor was related to his sickle cell disease.

I think this patient is an illustration of not only someone who has lived to age 52 with sickle cell disease, with relatively minimal difficulties, but in spite of that has had many of the complications that are related to having sickle cell disease.

I would like to thank all of the panelists for their presentations and discussions, and those of you in the audience for your participation and attendance and your contributions.

panel

EDUCATION AND SICKLE CELL SERVICES AS AN INTEGRAL PART OF COMPREHENSIVE HEALTH

A. J. Henley -- moderator
Bertram Lubin, M.D.
Eleanor G. Goines
Sylvia Wooten, M.D.

MR. HENLEY: As all of you are aware, for a number of years sickle cell anemia has been treated in something of an isolated fashion. This was necessary to bring about the kind of attention that we wanted it to have. However, we now feel that sickle cell should be treated as a part of the entire comprehensive health care program. We have a panel today that is going to speak to you about some of the things that are happening in many of our programs which will demonstrate to you how this kind of program can be handled.

We will first hear from Dr. Bertram Lubin, Chief of Hematology, Children's Hospital Medical Center, Oakland, California. He will speak to you concerning some of the activities in his center.

DR. LUBIN: Thank you.

I would like to review several components of our sickle cell program at the Children's Hospital. Three years ago, we received a contract for sickle cell screening, counseling, and education. Since our program is located in a children's hospital, we were able to incorporate the activities of our clinic into a patient care setting. We have attracted many patients with sickle cell disease to our program and have provided a comprehensive approach to sickle cell screening, counseling, and education in the Bay area. As a result of our collaboration with Dr. William Mentzer at the San Francisco General Hospital, our target population encompasses the entire Bay area.

We have focused our screening efforts on young children. In this way, we hope to provide early identification of sickle cell disease. Primarily, we screen children in preschool programs, and we also screen cord blood samples. For the purpose of this discussion, sickle cell disease will include homozygous SS (sickle cell anemia), SC disease, and S beta-thalassemia.

When we test young children, we screen for abnormal hemoglobins and iron deficiency anemia. We have included detection of iron deficiency in our screening process since approximately 30 percent of our target population is anemic. In addition, we test all children, regardless of race. We also have the capability to treat iron deficient children when necessary.

From July 1, 1973, to March 31, 1976, we screened approximately 24,396 people at the Children's Hospital. The results (see Table 24) are divided into normal AA patterns (21,914), traits (2,174), and disease (308). The number of sickle cell trait -- C trait, alpha- and beta-thalassemia trait -- are indicated. We identify individuals with alpha-thalassemia trait in cord blood samples where Bart's hemoglobin is detected. Beta-thalassemia trait is confirmed by decreased red cell size (mean corpuscular volume), and by elevated A_2 hemoglobin measured using a microcolumn technique.

Table 24. Sickle Cell Screening Program
July 1, 1973, to March 31, 1976.

	HEMOGLOBIN	NUMBER
NORMAL	AA	21,914
TRAIT	AS	1,420
	AC	550
	α-thal	74
	β-thal	111
	Other	19
	Subtotal	2,174
DISEASE	SS	173
	SC	77
	S-thal	43
	SHPFH	3
	Other	12
	Subtotal	308
Total number screened		24,396

The "other" category includes a variety of hemoglobin traits, both alpha chain and beta chain defects, which have been characterized by Dr. Thomas Bradley at the Veterans' Hospital in San Francisco and by the Center for Disease Control. The number of individuals with disease (308) does not include newly diagnosed patients, but represents the number and distribution of patients followed at Oakland's Children's Hospital. An additional 70 patients with disease are followed by Dr. Mentzer at San Francisco General Hospital.

A major goal of our educational program is to reach physicians who are taking care of patients with sickle cell disease. If the physician is not familiar with the appropriate diagnostic and therapeutic approaches, patient care will suffer. Physician education is provided by direct communication, formal lectures, community workshops, and teaching seminars.

In Table 25 I have indicated the sites where screening was performed last year. These figures demonstrate our emphasis on young children. In each location, sickle testing, counseling, and education were incorporated into a comprehensive health care program. We also placed emphasis on newborn screening (2,850). Because of the success of this cord blood screening program, we have expanded into several other hospitals in the Bay area. We plan to screen 7,000 newborns in the coming year. This will be our primary target population.

Child care centers are another target population for screening. We emphasize the child care centers because, in addition to early detection of sickle cell disease, we will also identify children who have an iron deficiency.

Among other groups, community organizations have requested sickle cell screening, counseling, and education programs. These are primarily adult groups. We emphasize sickle cell education for the community groups. We hope to get adults to consider the advantages, and perhaps the disadvantages of being screened. If adults decide to have the test, we hope they understand its significance. Special considerations are given to the genetic implications of sickle cell disease.

The following table indicates the number of newly diagnosed patients since we started our program at the Children's Hospital Medical Center:

Table 26. Newly Diagnosed Patients

Sickle Cell Anemia	22
Sickle Cell Hemoglobin-C	26
Sickle Cell S-thalassemia	12
Other	7
TOTAL	67

Table 25. Testing Locations

Test Sources	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	TOTAL
Children's Hospital Medical Center	901	618	544	448	2,511
San Francisco General Hospital		153	527	594	1,274
Newborns	718	691	655	786	2,850
Child Care Centers		114	155	836	1,105
Others	487	596	750	955	2,788
TOTAL	2,106	2,172	2,631	3,619	10,528

The patients with sickle cell anemia were primarily children under age four who were screened either in the hospital or in health care centers. Eight of the sickle cell hemoglobin-C patients were over age 30. Appendectomies had been performed on many of the other patients with sickle cell hemoglobin-C disease. Could these have been vaso-occlusive crises?

Once a patient is diagnosed as having sickle cell disease, we maintain an ongoing relationship with the child's physician. We offer the physician the opportunity to participate in our program, and try not to take the patient away from the private doctor. We continue to follow the private patients on an outpatient basis thoughout the year and during hospitalizations. Those patients with homozygous sickle cell who do not have private physicians are followed every six weeks in the sickle cell clinic. Those with SC disease are followed every three months unless they have problems that require more frequent followup.

Moving now to newborn screening, Table 27 is taken from an article in the New England Journal of Medicine in which Dr. Motulsky estimates the incidence of various abnormal hemoglobins among United States Blacks at birth. Alpha-thalassemia trait should be added to the list. We have found that six percent of our Black newborns have alpha-thalassemia trait. We feel it is important to notify the pediatrician taking care of this child and inform him that the child will have a persistent, mild microcytic hypochromic anemia.

Table 27. Estimated Frequencies of Hemoglobinopathies Among United States Blacks at Birth

Trait Frequencies	
Hb AS	8%
Hb AC	3
β-Thalassemia trait	1.5
Hereditary persistence of Hb F	0.1
Sickling Disorders	
Hb SS	1:625
Hb SC	1:833
Hb S-β Thalassemia	1:1,667
Hb S-Persistence of Hb F	1:25,000
Other Disorders	
Hb CC	1:4,444
Hb C-β Thalassemia	1:4,444

Figure 72 has been prepared from an actual cellulose acetate and citrate agar electrophoresis. Both of these strips are purchased from Helena Laboratories. These techniques are very reproducible, reliable, and easy to perform. We use cellulose acetate because we are interested in Bart's hemoglobin. We use the citrate agar because it provides a clear separation between hemoglobin F and S, whereas in cellulose acetate, the F and S bands are next to each other.

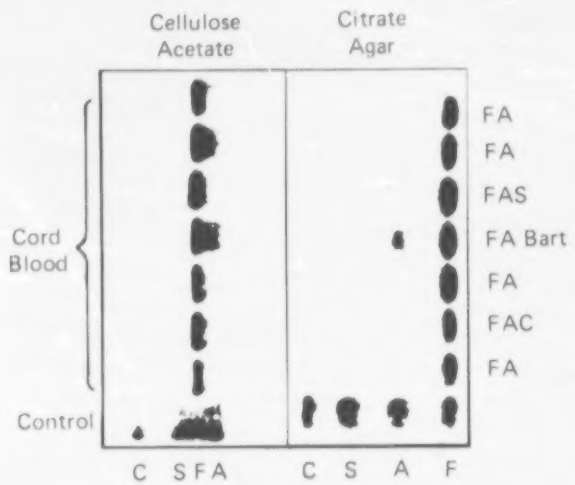


Figure 72. Cellulose acetate and citrate agar electrophoresis.

I feel that early identification and early education of the family are very important. For instance, we are currently evaluating a pneumococcal vaccine that may be of value in treating young children. Over the past year, we have immunized 76 children with an octovalent pneumococcal vaccine. We have not had an episode of pneumococcal sepsis in any of these patients.

We had had four episodes of pneumococcal septicemia in an unimmunized group of 125 patients. Two children have died from pneumococcal septicemia. All four of these were pneumococcal types present in the vaccine. I do not think we can draw firm conclusions from our preliminary study, but our results indicate

that this approach should be thoroughly investigated since pneumococcal sepsis is one of the major causes of death in sickle cell disease in the first three years of life.

Dr. Serjeant mentioned the problems of interpreting the citrate agar in the newborn period. If the quantity of hemoglobin A is greater than S, then the child has sickle trait. If the quantity of hemoglobin S is greater than A, then the child has sickle-beta-thalassemia. Since the quantity of nonfetal hemoglobin is small in cord blood, it is important to repeat the electrophoresis at six months of age on all newborns when the electrophoretic pattern has both hemoglobin A and S.

Table 28 shows the results of our cord blood screening to date. From a total of 5,407 samples, we found 134 sickle cell traits, 55 hemoglobin-C traits, 74 alpha-thalassemia traits, 5 homozygous sickle cell disease, 2 sickle cell hemoglobin-SC disease, 4 homozygous-CC disease, and 3 sickle cell-beta-thalassemia. All samples other than the normals were repeated and confirmed. This study was done at one hospital in the East Bay area. Fifty percent of the children born in this hospital were Caucasian. Therefore the population at risk was approximately 2,500. The hospital wanted the test done on all newborns, regardless of race. We did not find a white child with sickle cell disease, but identified two white children with sickle cell trait, two with fetal hemoglobin variants, and two with alpha chain variants.

Table 28. Cord Blood Screening
July 1973 to March 1976

Hemoglobinopathy	Number
FA	5,088
FA + Bart's	74
FAS	134
FAC	55
FS	5
FC	4
FSC	2
FSA	2
FF	18
AF	17
FA + Slow Hb	4
FA + ?	1
F + ?	2
FF (SA)	1
TOTAL	5,407

As I mentioned earlier, we screen for anemia at the same time we screen for hemoglobin abnormalities. This is accomplished by analyzing a microsample of blood in a Coulter Model S Counter. This machine determines the hemoglobin, red cell count, hematocrit, and red cell volume (MCV).

Figure 73 indicates the hemoglobin results of 5,000 samples from a pediatric population. And as you can see, 80 percent of the samples had hemoglobins that were 10.7 g percent or greater, and 20 percent were anemic with hemoglobins below 10.7 g percent. The most likely cause of the anemias was iron deficiency. Iron deficiency reflects nutritional inadequacies which, under certain circumstances, may have an effect on a child's subsequent growth and development.

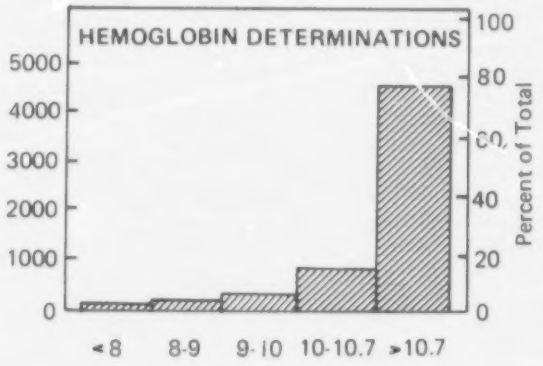


Figure 73. Hemoglobin determinations from 5,000 samples from a pediatric population.

In addition to the hemoglobin value, we also look at the mean cell volume (MCV). (See Figure 74.) We considered 76 μ^3 as a cut-off point, since the mean age of the test population was six years. Twenty-two percent of the results were below 76 μ^3. A low MCV can be seen in iron deficiency anemia, alpha-thalassemia trait, and lead poisoning.

If you are using the MCV as a screening tool, you must recognize that the normal MCV values in children are different from the normal MCV values in adults.

A study was performed by Dr. Koerper et al. at the University of California at San Francisco on a normal group of children in

whom the presence of an iron deficiency and thalassemia trait had been ruled out.* Between 10 and 17 months, the lower limit for an MCV was 70 μ^3; between 1-1/2 and 4 years it was 72 μ^3; and between four and seven years it was 76 μ^3.

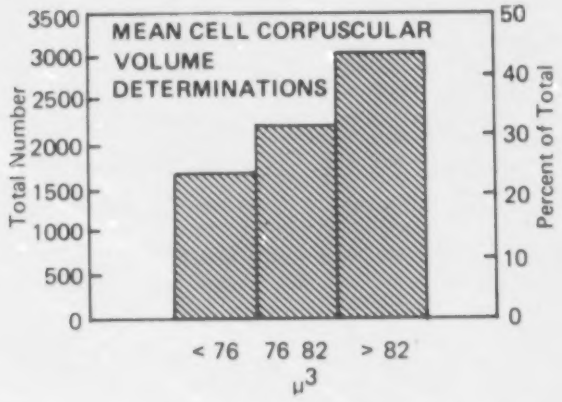


Figure 74. Mean cell corpuscular volume determinations.

To obtain more information from the original blood sample, we plan to measure red cell free erythrocyte protoporphyrin (FEP). The FEP level is elevated in iron deficiency and lead poisoning, but normal in thalassemia trait. If a child has a low MCV and an elevated FEP, he may have either lead poisoning or iron deficiency. If a child has a low FEP and a low MCV, it is most likely thalassemia trait. If hemoglobin A_2 is elevated, it is beta-thalassemia trait. If hemoglobin A_2 is normal, a diagnosis of alpha-thalassemia trait is made. If we were fortunate enough to have tested the child in the newborn period, the presence of Bart's hemoglobin would have established the diagnosis. This flow diagram may be used in future evaluations.

I suspect that the FEP measurement will be very helpful. On the same microsample, we will have a hemoglobin electrophoresis, an MCV, a hemoglobin, and FEP. These measurements will increase the information obtained and benefits provided in our sickle cell screening program.

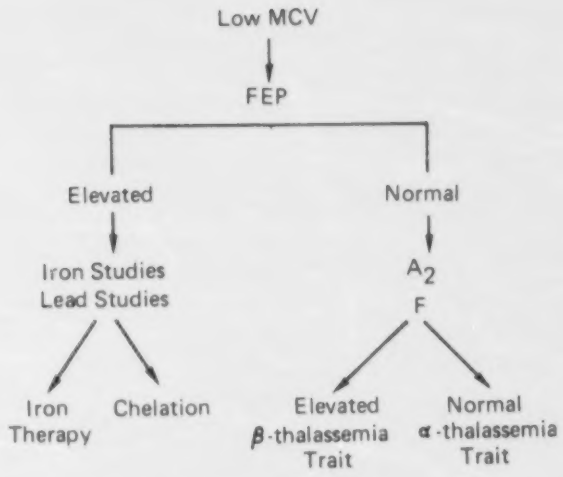


Figure 75. Flow diagram for use in evaluations.

In summary, our program involves patient care, physician education, cord blood screening, and screening for anemia.

QUESTION: You said you were getting six percent incidence of alpha-thalassemia in cord blood screening.

DR. LUBIN: The incidence of Bart's hemoglobin in newborn Blacks ranges from 3 to 10 percent. When we identify Bart's hemoglobin in the newborn period, we should also measure the mean corpuscular volume. If the mean corpuscular volume is normal (>104 μ^3), then the presence of Bart's hemoglobin indicates the silent carrier. This would not be a clinical problem. If the MCV is low and Bart's hemoglobin is present, a diagnosis of alpha-thalassemia trait can be made.

DR. REID: In terms of the studies you have done with pneumococcal vaccine with octovalent vaccine, what about the controls or the patient who did not get the vaccine in the age group?

DR. LUBIN: What we did was determined by the amount of vaccine available. We administered vaccine to consecutive patients until we used up the vaccine. There was enough for

*Koerper, M., et al., "Developmental Change in Red Cell Volume: Implication in Screening Infants and Children for Iron Deficiency and Thalassemia Trait," Journal of Pediatrics 89: 580, 1976.

75 doses. We found that after age one patients with sickle cell disease had a normal antibody response.

As a control group, we had some children with spherocytosis who had had their spleens removed, and they also responded with an antibody. Out of the unimmunized population (125 patients), there were four episodes of pneumococcal septicemia, all of the types contained in the vaccine, and two of those patients died. Both of the patients who died were started on penicillin treatment immediately upon arrival at the hospital. Within four or five hours they died.

QUESTION: Is your screening program in California interfaced with the federal EPSDT screening program?

DR. LUBIN: Yes, where possible. We have some state support to provide education for people interested in sickle cell. Our program is available, obviously, to anyone who wants to have the testing done.

QUESTION: I have a second question, then. Does the California EPSDT program stipulate whether electrophoresis is preliminary?

DR. LUBIN: Yes. Electrophoresis is the preliminary method.

MR. HENLEY: I would like to thank Dr. Lubin for accomplishing his mission.

Next we will hear from Ms. Eleanor Goines, Project Manager of the DePaul Hospital Sickle Cell Clinic.

MS. GOINES: Many years ago General Electric had as its motto, "Progress, our most important product." As an inquiring youth, I wondered, if progress is the most important product, then what is the most important tool? I soon began to speculate that probably the most important tool is education. And it seems apparent to me that the conference planners had similar thoughts regarding education in that the conference theme is "Education Today, Better Health Tomorrow." For certainly, health education is really a form of preventive medicine.

Perhaps before I go further I should define education as I see it. Education is a systematic process of training and developing knowledge, skills, mind, character, et cetera. Education has achieved its goal when the student has developed favorable health attitudes, behavior, and a better understanding, in our case, of hemoglobinopathies as a result of this systematic process.

Since 1972, we in the federally funded sickle cell clinics have been saying that sickle cell services should be broadened. Some of us have suggested that sickle cell clinics become an integral part of comprehensive health centers. This suggestion is certainly harakiri for some of us, yet, our primary concern is for better, total patient care. Ideally, comprehensive health care for sickle cell patients is the best way to serve them.

Presently, the federally funded sickle cell clinics are only providing screening, education, counseling, and referral services. The comprehensive program, on the other hand, would provide for the medical, psychological, and social problems of the patient. In addition, there would be ongoing services for other members of the family. In particular, there would be an attempt to assist the family in coping with medical problems.

All comprehensive health services should encompass the four "A's" of health care. The first "A" is accessibility. Services should be accessible to the people you plan to serve. The second "A" is acceptable. The services should be acceptable to the community or society you plan to serve, taking into consideration the location of the community, what the community wants, what the community needs to know about sickle cell anemia, and what its attitudes are toward this disease. The third "A" is accountable. Sickle cell services via comprehensive health centers must be accountable to the consumers that we purport to serve. The fourth "A" is accredited. Community health care programs must be accredited. No longer can we consciously encourage the operation of poorly administrated health care programs in our communities, for it is true that good health care is a right, not a privilege.

It is our hope that as a result of a link-up of sickle cell services with comprehensive health centers these services will become more readily available to a larger segment of the population.

Let us go back to the second "A," acceptability by the community. Education plays a vital role in shaping the attitude of a community

toward sickle cell disease. I define sickle cell disease as including sickle cell trait, sickle cell variants, as well as sickle cell anemia. Sickle cell education should not be selective in terms of racial or professional groups. It is important that all persons -- irrespective of race -- understand what sickle cell disease is. Why? Because we live in a facsimile of an integrated society, hence, "getting to know you, getting to know all about you, getting to like you, and hoping that you like me" -- understanding you, and understanding that you are different from me. We at DePaul Hospital Sickle Cell Clinic have refused to provide education in integrated schools where we are told we can only provide educational programs for Black students.

Let it be resolved that the attendees of the First National Sickle Cell Conference leave here with a renewed desire to integrate sickle cell services into ongoing comprehensive health centers.

MR. HENLEY: Thank you, Eleanor.

We will now hear from Dr. Sylvia Wooten, Chief of the Southwest Health Center, Washington, D.C.

DR. WOOTEN: When one thinks of a comprehensive health program, one usually envisions a medical center that houses all of the major specialty clinics in areas such as internal medicine, obstetrics and gynecology, pediatrics, and possibly, surgery. Many other ancillary services, such as podiatry and dermatology, social services, nutritional services, laboratory and X-ray facilities, pharmaceutical, and possibly dental and visiting public health nursing services may be included in this complex. Our own center offers all of these services except for a surgical clinic.

Rarely is it ever mentioned that comprehensive services for sickle cell anemia and its variants are available. Comprehensive services for sickle cell anemia and its variants should include education on the etiology and pathogenesis of sickle cell disease and related hematological conditions; voluntary, accurate, and confidential blood screening; and follow-up on all affected individuals with professional genetic counseling.

Few comprehensive health centers offer these services. However, thanks to the federal grants of recent years, this deficiency in services has been partially offset by the establishment of about 31 sickle cell screening and education clinics, and approximately 15 sickle cell centers around the country.

The incorporation of complete sickle cell services into the neighborhood comprehensive health care centers is long overdue. The term comprehensive implies complete, all inclusive, and in-depth involvement. The organization that wears the comprehensive title is expected to be a full service center, capable of supplying outpatient needs from the cradle to the grave, so to speak.

At the comprehensive health care center, the hypertensive patient is counseled on his dietary and emotional habits. The obese patient is cautioned to cut back caloric intake. The diabetic is taught how to self-administer insulin and how to manipulate the dietary exchange system. The adolescent is given sex education and a run-down on the available contraceptive devices, although most teenagers feel they do not need it until it is too late.

But what happens to the patient with a positive sickle cell diagnosis? All too frequently, nothing. Many private and public health physicians feel that it is either too bothersome or too complicated an issue to fully explain to the patient or parents since they may not understand the genetics. Some are ill-informed so that they thoroughly succeed in saturating the patient or parent with inaccurate information, thus engendering hostilities and undue anxieties.

Not infrequently, patients with only the trait are told they have the disease. This is unforgivable. It is the responsibility and obligation of the physician and his staff to acquire as much current and accurate information on sickle cell disease as possible. Sickle cell disease is a well-known mimicker of many other diseases and has been reported to affect practically every system of the body at some time or other. This is one of the reasons that those responsible for the delivery of primary care, particularly to Black people, should be throughly familiar with every aspect of this disease.

They should also be aware of the many unsubstantiated reports that attempt to implicate sickle cell disease and sometimes even the trait as the cause of bizarre symptoms. In the July 1975 issue of the Alabama Journal of

Medical Sciences, Marcel Lee Conrad tells of several investigators' reports of episodes of rhabdomyolysis with renal shutdown following severe exercise in subjects with sickle cell trait. This is a condition resulting from the rapid breakdown of striated muscle tissue, leading to renal failure, secondary to the inability of the kidneys to handle the excessive amounts of myoglobin released. A few of these subjects had a history of a preceding upper respiratory infection. However, there was no definite proof that these events were related to the sickle cell trait. Professional football players and Olympic athletes with sickle cell trait have undergone extensive, strenuous exercises at high altitudes under observation without ill effects.

Yoder, Tibesh, and Tuguchi reported in the February 1975 issue of the Ohio State Medical Journal the case of a 45-year-old Black male who was admitted to the Dayton, Ohio, Veterans' Administration Hospital on May 29, 1971, with a history of sickle cell trait and chronic alcoholism. This patient died from primary pulmonary hypertension with right ventricular failure, associated with liver cirrhosis and portal hypertension. According to the authors, both his chronic and acute medical conditions were believed to have played a role in stimulating a latent sickle cell trait into an acute disease condition. It was felt that alcoholism may have been the major factor in initiating sickling in this patient, leading to multiple pulmonary emboli and pulmonary hypertension.

The autopsy revealed sickle cell thrombi in small pulmonary arterioles. Alcohol is known to cause dehydration, which can intensify the sickling process. However, to assume the sickle cell thrombi that were found in this patient's pulmonary arterioles on autopsy were formed prior to death and not as a result of the postmortem conditions may, in my opinion, be misleading. Acidosis and stasis, which are a part of the postmortem process, can initiate the formation of sickle cells after the death of a person with the trait. Merely finding sickle cell thrombi on autopsy does not necessarily substantiate the authors' conclusion.

Another report, which may or may not implicate homozygous sickle cell disease in a sensorineural hearing loss of some Jamaican patients, was presented by Serjeant, Normal, and Todd in the April 1975 issue of Journal of Laryngology and Otology. They commented on a recent study which demonstrated a significant increase in the incidence of abnormal audiograms in Jamaican sickle cell anemia patients. Audiometric loss was appreciated at both extremes of the hearing range but was most marked at higher tones and appeared gradual in onset.

One possible theory offered was that the expansion of the narrow space in the petrous temporal bone led to a narrowing of the internal auditory canal, resulting in the compression of the stato-acoustic (8th cranial) nerve. However, this hypothesis was not supported by subsequent study. No correlation could be found between hemoglobin and reticulocyte levels and the diameter of the internal auditory canal, as would have been expected if compensatory expansion of the narrow space in petrous temporal bone had resulted in the narrowing of the canal. In other words, if the patient's bone marrow was hyperplastic and expanding, thereby narrowing the internal auditory canal, you would expect a low hemoglobin and a high reticulocyte count. But there was no correlation in these patients. This gradual sensorineural hearing loss was thought possibly to be the sequel to sickling and sludging of red cells in the cochlear venous system with secondary anoxia of the hair cells and striae vascularis. However, this is an hypothesis, not a proven fact.

These cases are cited to reemphasize the point that the practitioner and all those responsible for managing and counseling the sickle cell patient must be alert to every new occurrence in the sickle cell field, for it is incumbent on them to differentiate fact from theory as they interpret these findings on behalf of the patient.

Successful psychosocial adaptation of the sickle cell patient is another extremely important aspect of the comprehensive approach to managing the sickle cell patient. What profit is there for a patient to successfully adapt to or overcome the organic limitations of his disease only to succumb to the sea of self-pity and self-doubt that always lurks on the periphery of all chronic diseases?

Many variables, such as the patient's own personality, the behavior and attitudes of his family members toward him and his disease, and his community's resources and responses vitally affect his psychosocial adjustment.

Coordinated effort on the part of the comprehensive health team should be made to assure that the patient receives accurate facts about his disease, anticipatory guidance, and intermittent counseling on an ongoing basis by a competently trained individual.

It is also the team's responsibility to help the sickle cell patient cope with the effects of his disease to the extent that he is limited only by the absolutely unresolvable realities of his condition. The patient should have the assurance that the physician and staff will be there to give sympathetic relief from his discomfort during periods of exacerbation of his disease. This lessens his hear of abandonment. Should the patient's condition warrant hospitalization, the comprehensive staff should act as liaison between patient, family, and the hospital. This, too, helps to decrease anxiety and feelings of isolation on the patient's part.

The parents and other family members must also be counseled on how to be supportive of the patient. They must be made aware of the times when it is better to listen to the patient and to allow him to ventilate his feelings of anger, jealousy, frustration, or whatever, and not cut him short in this process. However, the family must be cautioned against overprotectiveness. Parents must learn how to allay the child's fears without lying about or minimizing the true nature of his condition. Once the patient becomes aware that his feelings are not unusual and are even understandable, he can then be convinced of the folly of allowing these emotions to defeat any true progress he may be capable of achieving.

Other feelings to be dealt with are those of guilt. There may be guilt on both sides -- that of the parents who may feel directly responsible for having "passed on" a disease to one of their offspring, and that of the child who, especially if very young, may feel that his disease and its accompanying symptoms are punishment for his own misconduct or inappropriate thoughts.

Parents of sickle cell patients should encourage them to develop both their natural and their potential talents. A strong respect for the educational process should be instilled in these youngsters. If such a child later excels in a particular discipline, his reward is usually a strengthened ego and a healthy self-image.

When a particularly sensitive youngster is discovered, a comprehensive staff member should be assigned to monitor his psychological well-being. The staffer, himself, must be sensitive enough to recognize and interpret the social and psychological barometers of his patient. Self-esteem is one of the most important gifts that can be given to the sickle cell patient. Being able to help a younger individual or someone whose abilities in a particular area are not as great as those of the patient can go a long way toward ego-reinforcement.

Family counseling is another service that should be offered by the comprehensive health center. It can be just as important as individual counseling and should be available on a continuous basis through the years. It is impossible for the family of the sickle cell patient to assimilate all of the information pertaining to the patient's condition in just one session.

It is also unlikely that all of the potential problems will even be anticipated by the counselor or the family. Therefore, the counseling facility must be available at each turning point through the years. However, regular counseling sessions, strategically scheduled, should lessen the number of crisis-oriented sessions.

Since the comprehensive health care center is usually an integral part of a community sector, one of its many functions is to see that the surrounding neighborhood is also educated in the accurate facts of sickle cell anemia. The community health aide, the center's liaison with the local residents, is an excellent person to help fashion appropriate attitudes toward sickle cell anemia. If prejudicial attitudes can be altered in local communities, eventually entire cities, then states, and perhaps society in general will become politically motivated to enact protective legislation on behalf of not only sickle cell patients, but all citizens who may be incapacitated in some way.

Many communities have been successful in getting their legislators to support the "Hire the Handicapped" movement currently under way. In many instances, curbs of city streets, steps, doorways, and elevators of business and government buildings have been altered to accommodate wheelchairs. All of these changes are encouraging harbingers of growing attitudes that reflect the tolerance

and sense of fair play developing in the citizens of this country.

The comprehensive health care center may be one of the most important institution underlying the surge of this new attitude. I am optimistic about future gains in this direction.

MR. HENLEY: The panel will now entertain any questions you might have.

QUESTION: I was wondering if the panel members could depart for a moment from the internal comprehensiveness of the sickle cell services and deal briefly with the external environment, specifically, the health system's agencies or any new governmental programs, and how they function in the health milieu. Have any of you reached that point in your research?

MS. GOINES: Here in St. Louis there has not been any coordination between these agencies and our programs. Our funding thus far has been coordinated by the national sickle cell office.

However, in St. Louis we do have the closest thing to a comprehensive sickle cell program, because the State of Missouri provides for education, screening, and counseling. Some money was appropriated for treatment. In the State of Missouri, if patients go to our clinics and they are without health care insurance, we can refer them to some of the hospitals where the state has a contract, and they will be provided with hospitalization at no cost. So that is the closest we have come in terms of coordinating the comprehensive sickle cell program state-wide.

MR. HENLEY: If there are no other questions, I would like to give my thanks to the panel, and we will turn the program over to Dr. Harold Ballard, who will give the conference wrap-up.

conference wrap-up

CONFERENCE WRAP-UP

Harold Ballard, M.D.

I would like to highlight selected aspects of the topics that have been presented at this symposium. Sixty-six years ago, in 1910, Dr. William Herrick, a practicing cardiologist in Chicago, described the first case of sickle cell anemia in the United States. Herrick's description of the presence of peculiar, elongated, and sickle-shaped red blood corpuscles in a case of severe anemia had particular interest because of the association of a distinct morphologic abnormality of the red blood cell and the presence of clinical abnormalities in the patient.

During the six decades spanning the period from 1910 to 1970, a vast body of knowledge has been accumulated concerning molecular biology, pathology, pathophysiology, and clinical manifestations of sickle cell anemia. Among the important scientific observations occurring during this period, the following were of particular significance. First, was the discovery by Han and Gillespie in 1927 of the relationship between the shape change of the erythrocytes in patients with sickle cell anemia to the lowered oxygen tension. In a wet preparation of blood from a patient with sickle cell anemia that has been subjected to conditions of low oxygen tension, you will note that not all the cells are sickled. There are several cells that retain the bioconcave disc configuration. This is probably related to the higher fetal hemoglobin content of those cells.

The next observation of particular importance was the notation by Dr. Linus Pauling in 1949 that the hemoglobin from patients with these abnormal cells had a different electrophoretic mobility than normal hemoglobin. Because of the abnormal electrophoretic property of S hemoglobin, Pauling coined the term "molecular disease" for sickle cell anemia.

In the same year, Dr. Neel at the University of Michigan clarified the inheritance pattern of sickle cell anemia on the basis of family genetic studies. He advanced the hypothesis that the clinical benign condition represented the heterozygous state, whereas the homozygous state was responsible for the anemia of the patient with sickle cell disease.

We have all seen a pedigree of a man and woman, each of whom has sickle cell trait, showing the possibilities for the offspring. This mating will result on average in 50 percent of the children having S trait, 25 percent being normal and 25 percent having sickle cell anemia. What is important to know is that if one has four children, the inheritance pattern will not necessarily follow this diagram. It simply indicates that for any given pregnancy there is a 25 percent probability of the offspring being homozygous for sickle cell anemia, a 25 percent chance of being normal, and a 50 percent chance of inheriting the trait. It is perfectly possible to have two or three children, none of whom have sickle cell anemia, or two or three children, all of whom have sickle cell anemia.

In 1950, Harris demonstrated the physical reality of this abnormal electrophoretic property by showing that when cell-free solutions of hemoglobin S were deoxygenated, they became viscous, and displayed birefringence under polarized light. Under phase microscopy, this birefringence was shown to consist of spindle-shaped bodies, so-called liquid crystals or tactoids.

Finally, studies by Ingram in 1957 ascribed the difference in electrophoretic mobility to a charge difference caused by the substitution of a single amino acid valine for the normal glutamic acid at the sixth position from the N-terminal of the beta chain. It is this single, genetically controlled, molecular modification that permits deoxygenation to cause tactoids or gelling, and is responsible for all the clinical manifestations of sickle cell anemia.

During the first half of this decade, there was a surge of national interest in sickle cell anemia in part spurred by the federal government's commitment to expanded research in this disease. Special emphasis was placed on basic and clinical research, clinical application, training, education, laboratory testing,

and counseling. A major effort on the part of health educators addresses the misconceptions concerning the meaning of the sickle cell trait.

I would like to begin the wrap-up by reviewing the significance of the hemoglobin genotype AS, popularly known as sickle cell trait.

The term "trait" is used to describe a person who has inherited one gene for normal hemoglobin A from one parent, and one gene for S hemoglobin from the other parent. Electrophoresis of red cell hemolysate reveals hemoglobins A, S, A_2, and F. Hemoglobin S always constitutes less than 50 percent of the total hemoglobin.

The patient with hemoglobin S trait is asymptomatic under normal physiological conditions. There is no anemia or splenomegaly. The red blood cell survival is normal. The only persistent clinical abnormalities are renal in origin, and these consist primarily of a concentrating defect and occasional instances of painless hematuria.

The key to laboratory diagnosis of hemoglobinopathies is hemoglobin electrophoresis. In sickle cell anemia, the amino acid substitution that distinguishes it from hemoglobin A causes alterations in the overall charge of the molecules, which can be easily detected by electrophoretic techniques. Clearly, if the amino acid substitution is not attended by a change in charge, variants may have an electrophoretic mobility similar to normal hemoglobin.

It is of clinical importance to appreciate that a hemoglobin electrophoretic pattern showing the majority of the hemoglobin migrating as S cannot be accepted as proof that the patient has homozygous S disease. Despite the simplicity of the electrophoretic abnormalities associated with sickle cell anemia, there are a number of genetic abnormalities which, when inherited along with a single gene for hemoglobin S, can produce an electrophoretic pattern identical to, or at least with only subtle differences from, sickle cell anemia. These include sickle cell beta-thalassemia, sickle cell/high persistent fetal hemoglobin, and sickle cell/Hb D disease.

Accuracy in diagnosis is important: first, in order to give accurate genetic counseling; and second, because of the different prognoses implicit in a diagnosis other than homozygous S. Based on the fact that deoxygenated hemolysates of hemoglobin S form tactoids and have a uniformly low solubility with respect to hemoglobin A, one generally follows hemoglobin electrophoresis with solubility studies.

As regards the pathophysiology of sickling, the most unique rheological property of the normal erythrocyte is its fluidity, in the sense that it can be deformed continuously and rapidly during flow, squeezing through passages which have narrower cross-sections than itself. The erythrocyte has the reheological properties of a fluid pellet. Deformability of normal erythrocytes, which is necessary for their normal survival and for adequate flow of blood in the microcirculation, depends upon the maintenance of a semi-fluid state within the cells, as well as a flexible membrane.

Oxygenated blood from patients with sickle cell anemia has an increased viscosity, associated primarily with the presence of deformed cells, the so-called irreversibly sickled cells. This increased viscosity is presumably due to the reduced membrane flexibility of the deformed cells and the increased internal viscosity associated with a high mean corpuscular hemoglobin concentration.

A striking feature of the blood smear in most instances of sickle cell anemia is the particularly elongated, pointed, and deformed cells, which are referred to as irreversible sickle cells (ISC), because they retain their deformed shape despite oxygenation.

In addition to tactoid formation, an important property of sickle hemoglobin is the formation of gels at very low concentrations of hemoglobin. Gelling of deoxygenated hemolysates of hemoglobin S is a manifestation of the tendency of deoxyhemoglobin S to aggregate in concentrated solutions. When a sample of hemoglobin S is deoxygenated, it forms a gel when the concentration of hemoglobin S is at least 24 grams percent. An equal mixture of hemoglobin A and S, under similar conditions, gels at a higher total hemoglobin concentration (about 30 grams percent), indicating a lesser tendency for the hemoglobin molecules to form organized crystals.

Although the precise organization is unknown, it is clear from clinical and laboratory investigations that when the red cells of patients whose hemoglobin genotypes contain hemoglobin S in combination with other hemoglobin variants are lysed and deoxygenated, the nature of the variant hemoglobin determines the extent of its participation in the formation of deoxyhemoglobin gels.

The severity of the clinical syndromes accompanying the simultaneous presence of hemoglobin S with another hemoglobin variant has been well-correlated with the physicochemical properties of these mixtures. For example, a mixture of hemoglobin S and hemoglobin O (Arabia) has a lower gelling concentration than homozygous S.

In contrast, a mixture of hemoglobin S and hemoglobin F has a higher gelling concentration than hemoglobin S and hemoglobin A. This higher gelling concentration reflects the nonparticipatory role of hemoglobin F in gelation with deoxygenated Hb S, whereas the lower minimum gelling concentration for Hb S/O reflects the facility with which hemoglobin O (Arabia) will copolymerize with hemoglobin S. Clinically this is manifested by severe clinical symptomatology in subjects with Hb S/O and relatively benign disease in patients with Hb S/HPFH. The higher the minimal concentrations required, the lower the tendency to gelling. The lower the minimum concentration, the greater the tendency toward gelling.

In contrast to erythrocytes that remain "sickled" only when deoxygenation is maintained, some of the sickled red blood cells retain their deformed shape even after oxygenation. A typical smear of oxygenated blood from a patient with sickle cell anemia shows these deformed, elongated, and densely-stained cells which have been called irreversible sickle cells. The presence of increased numbers of these cells, in some instances, tends to correlate with the rate of cell destruction, increased viscosity, diminished filterability, and decreased deformability. The implications of these in vitro and in vivo observations allow us to understand to a considerable degree the clinical phenomena of sickle cell anemia as it affects various organ systems.

According to one molecular hypothesis for sickling, reduced hemoglobin S molecules have a valine site as well as a complementary site. Reduced Hb A has only a complementary site. In order for sickling to occur, a deoxygenated molecule needs both a complementary site and the valine substitution. Only reduced molecules of hemoglobin S contain these two requisites for polymerization and gel formation.

Conditions favoring sickling are high cellular concentrations of hemoglobin S, low oxygen tension, acidosis, and stasis in an unfavorable environment. The process is self-perpetuating because vascular occlusion produces stasis and ischemia, with a decrease in both oxygen tension and pH, which in turn produces more sickling. At times there is tissue damage, a more permanent type of vascular occlusion, and ultimately infarction and fibrosis of tissue.

The clinical and hematologic manifestations reflect two processes: first, severe hemolysis with the compensatory mechanism resultant therefrom and second, widespread vaso-occlusive phenomena involving many tissues and organs. The clinical entity sickle cell anemia is a multi-organ disease complex with protean clinical manifestations. The manner in which the basic defect in the red blood cells produces the ultimate pathologic picture is not known, although many notions have been put forth. The gradual attrition suffered by patients with this affliction derives from luminal occlusion of small vessels by sickle cells in various stages of reversible and irreversible deformation.

Grand rounds discussions have focused on both the pediatric and adult patient with sickle cell anemia. These rounds have served as a basis for a rather comprehensive overview of the clinical manifestations and have also served to illustrate that individuals with sickle cell anemia may have both acute and chronic illnesses unrelated to the mutant hemoglobin.

In other words, patients with sickle cell disease are not immune to other disorders. For example, the young woman with sickle cell anemia who presents with abdominal pain may have an ectopic pregnancy, torsion of an ovarian cyst, or appendicitis. One must be constantly vigilant so as not to misdiagnose a serious but fully remediable, unrelated illness.

Patients with sickle cell anemia experience four types of crises: aplastic, sequestration, vaso-occlusive, and hyperhemolytic. The aplastic crisis results from diminished red cell production superimposed on the usual rapid destruction of red blood cells. Peripheral blood films of patients admitted to the emergency room should be examined very carefully for the presence of poly-chromatophilia. Its absence should alert one to the possibility of an aplastic crisis.

The sequestration crisis results from sudden pooling of vast amounts of blood in the spleen. It is the most immediately dangerous crisis in the life of the young child with this disease. It must be recognized and treated promptly. The vaso-occlusive crisis is the most common and the most painful. It is secondary to aggregation of sickle cells and vasospasm.

Crises of all types are more common in children. The symptomatology accompanying the vaso-occlusive crisis follows a more or less consistent pattern for any given individual. In most instances, vaso-occlusive crises are not associated with immediate residual defects. Crises are usually self-limited, and most symptoms disappear with the termination of the crisis. Lastly, not all patients with sickle cell disease will have severe, debilitating crises.

The critical period for the development of sepsis in the young child appears to coincide with the onset of functional asplenia. Functional asplenia is reflected peripherally by the appearance of Howell-Jolly bodies in the red blood cells. Again, examination of the peripheral blood may be of value.

If one analyzes the frequency of hospitalizations for sickle cell anemia, it is surprising to note that the great majority of hospitalizations are accounted for by a minor population of sickle cell patients.

The hematologic findings in sickle cell anemia are essentially those of a normochromic, normocytic anemia. The peripheral blood smear reveals anisocytosis, poikilocytosis, polychromatophilia, and variable numbers of sickled forms. Other laboratory findings include an elevated reticulocyte count, decreased osmotic fragility, increased mechanical fragility, leukocytosis, a low sedimentation rate, and erythroid hyperplasia in the bone marrow.

There are many concomitants of sickle cell anemia. The more common ones include cholecystitis with cholelithiasis, priapism, gross hematuria, nephritis, nephrotic syndrome, cor pulmonale, hemochromatosis, cerebrovascular accidents, osteomyelitis, aseptic necrosis, leg ulcers, and diminished visual acuity.

In regard to roentgenologic findings, skull X-rays generally reveal "hair on end" appearance, compression fractures of the vertebrae, bone infarcts, aseptic necrosis, and calcification in the spleen. The "hair on end" appearance is the result of extreme hyperplasia of the marrow that expands the tables of the skull.

You heard a very interesting paper detailing the ocular manifestations of sickle cell anemia. These include tortuosity of vessels, transient migratory constriction, vascular occlusion, and the most severe complication, retinal separation or detachment. These findings are more common in patients with SC disease, perhaps as a result of the increased viscosity due to the increase hematocrit in these patients.

The treatment of sickle cell anemia should encompass three major areas: general support, management of crises, and long-term therapy. Problems in management depend in part upon the age group. As we mentioned earlier, crises of all types are more common in the first decade, and infections are particularly prominent. In very small children, illness must be detected early and signs and symptoms must be explained to the parents. Parent education is mandatory if we are to provide small children with adequate care. This is of particular significance in the prompt diagnosis of infection which will frequently spell the difference between life and death.

Prophylactic medical care of infants with sickle cell anemia can prevent many needless and potentially lethal complications of the disease. Children's very special problems revolve around the serious infections they encounter, particularly pneumococcal meningitis, in which the mortality in sickle cell anemia is highest in the first two years of life. To improve our track record, it is essential that

management of children with SC include neonatal diagnosis. This is extremely important because if the disease is not diagnosed in the early months of life, then it is very difficult to be aware of these early complications that lead to high infant mortality. Once the diagnosis is established, comprehensive medical follow-up is mandatory if we are to prevent catastrophes. As Dr. Pearson mentioned, unless comprehensive, continuing medical care is available, neonatal diagnosis is of dubious value.

Two mechanisms have been postulated as the pathogenesis or the reason for children's increased susceptibility to infection: a defect in heat labile opsonins for pneumococci, and a defect in the alternate pathway of activation of serum complement. The critical period for young children appears to be between the ages of six months and five years. As was also mentioned, a significant cause of mortality in African children appears to be malaria. Malarial prophylaxis has been of great value in these individuals.

In adolescents, special problems are also present in management, primarily psychosocial and adjustment problems. They relate primarily to progress in school, anticipation of marriage, ability to secure meaningful work, ability to perform adequately in jobs, morbid fears, and pregnancy. All of these concerns tend to create great emotional problems. For adults, the principal problems are end organ failure primarily involving lung, heart, kidney, and liver.

Some of the preventive measures that an SC patient might take advantage of include:

- Avoid exposure to extremes in temperature.
- Seek prompt medical attention for infection.
- Avoid underwater sports and mountain climbing.
- Arrange for periodic health check-ups.
- Birth control pills would appear to be safe.

Management during acute crises has not really changed very much in the last two decades. It is primarily supportive and palliative, for example, reassuring the patient, administration of analgesics and sedatives, and prescriptions for bed rest, hydration, oxygen, or antibiotics for infection. Be aware that sickle cell disease patients are not immune to other morbid states which result in acute surgical abdomens.

Many pharmaceutical agents have been utilized in an attempt to ameliorate crisis, attesting, I think, to the inefficacy of any of these particular preparations. In the last decade particular attention has been directed to urea therapy and cyanate. A double-blind controlled clinical trial has been completed employing urea therapy, and the results of that trial demonstrated no striking differences in benefit to patients receiving urea. In other words, there is no benefit accruing to the patient who receives urea therapy.

Most recently, cyanate has been the subject of intensive trials. Cyanate administered orally carbamylates the amino terminal valine residues of the beta chains of hemoglobin. Sickling is prevented in 80 percent of the cells. It alters the oxygen dissociation curve with a shift to the left, and increases the erythrocyte survival time.

A controlled clinical trial with cyanate has recently been completed, and the results of that study seem to indicate there is no advantage to the administration of cyanate as regards the amelioration of vaso-occlusive crises. In addition, cyanate has some side effects which are significant, including peripheral neuropathy, impaired nerve conduction, inhibition of protein synthesis, and more recently, cataract formation.

The indications for transfusion are: elective or emergency surgery, aplastic crisis associated with severe anemia, serious infections, severe recurrent crises and/or pain where other measures have failed, and severe anemia in a pregnant woman at term. In some instances hypertransfusions or limited exchange transfusions may be indicated. These instances include pregnancy, crises with central nervous system defects, and complications of surgery and anesthesia.

The rationale for these transfusions is: immediate reduction in the percentage of

sickled cells in the circulation, increased O_2 carrying capacity, and a reduction in the recipient's erythropoiesis which diminishes the number of cells containing hemoglobin S entering the circulation. Frozen and thawed red cells is the preparation of choice. It reduces the incidence of viral hepatitis, minimizes the potential for developing platelet and/or leukocyte antibodies, and reduces the incidence of all untoward reactions.

The intercritical period management consists of periodic physical evaluations, periodic hematologic appraisal, prompt recognition of infection, provision of good nutrition, and adequate utilization of supportive resources, for example, mental hygiene clinics, social service, and so forth. However, prevention of crisis is the ultimate objective.

One objective of the psychosocial approach is to assist individuals in obtaining optimum adaptation to their individual stresses. Another objective is to determine how effectively individuals utilize counseling and other resources in dealing with problems in the following areas: housing, employment, psychosexual conflict, interfamilial relationships, relationships with peers, and interpersonal relationships. The psychosocial approach attempts to provide guidance and counseling in all of the above areas. Psychosocial management will entail individualized counseling, evaluation of attitudes, evaluation of adaptive and maladaptive coping mechanisms, and pinpointing pyschosocial conditions which may precipitate or extend crisis.

The overall management is multidisciplinary, consisting of education, counseling, prevention, social services, vocational guidance, adequate usage of subspecialty resources, and clinical support during the intercritical period and during periods of acute medical and surgical disability states.

In regards to the natural history of the SC patient, the prognostic expectations for mortality and morbidity in patients with sickle cell anemia have improved significantly during the last 25 years. Expectations for an infant born with sickle cell anemia in the 1970's obviously differ from those of infants born during the 1940's. The last decade has been characterized by accelerated developments in the area of sickle cell anemia research. Basic and clinical research is now in full swing.

Current investigative efforts are addressing multidisciplinary approaches to understanding natural history, clinical manifestations, and pathology and pathophysiology at the vascular, organ, tissue, cellular, and molecular levels. The multi-organ clinical and pathological manifestations are being documented in greater depth and with increasing sophistication.

The problems of job and insurance discrimination are being addressed and misconceptions concerning both the trait and the disease are being dispelled. In addition, more effective education and counseling is now available. Improved methods of detecting abnormal hemoglobins are being studied and, hemoglobin structure is being more intensively investigated. Antenatal diagnosis, though considered experimental today, is on the scene, and plans for addressing the many controversies that will be generated by the introduction of this procedure are presently under way.

Fortunately, for the many Americans who have sickle cell anemia, a rapidly changing social climate is creating an awareness of the magnitude of the problem. As a consequence, more federal funds and public contributions are being channeled into needed research. Physicians and health officials are finally recognizing the significance of sickle cell disease.

The major thrust of future efforts will address basic molecular events, for it is only through improved understanding of the molecular events that precede and occur during the sickling phenomenon that bioengineering will be able to provide the promise of cure.

We can all take pride in the vigorous national programs addressing education, clinical care, and research for sickle cell anemia. We can justifiably look forward to the future with optimism. Hence, since Herrick's initial report in 1910, it is evident that we have traveled a great distance, and with the vast volume of knowledge that has been accumulated, we can look forward to a tomorrow when the lives of patients with sickle cell anemia will be made more comfortable, and longevity will be appreciably extended.

I think we all owe a great debt of gratitude

to Dr. Clarice Reid and the National Heart, Lung, and Blood Institute for this most interesting and provocative educational experience. I am sure we will leave St. Louis with a much greater understanding of the directions we are moving in, in the area of sickle cell anemia.

appendix

CONFERENCE PARTICIPANTS

Harold Ballard, M.D.
Associate Chief of Hematology
Manhattan VA Hospital
New York, New York

John Bertles, M.D.
Director, Hematology Division
St. Luke's Hospital Center
New York, New York

James Bowman, M.D.
Director, Comprehensive Sickle Cell Center
University of Chicago
Chicago, Illinois

Naomi Chamberlain
Educator-Consultant Expert
National Institutes of Health
Bethesda, Maryland

Delores Duncan, M.S.W.
Comprehensive Sickle Cell Center
Howard University School of Medicine
Washington, D.C.

William F. Friedman, M.D.
Professor of Pediatrics
Chief, Pediatric Cardiology
University Hospital
San Diego, California

Marilyn H. Gaston, M.D.
Director, Comprehensive Sickle Cell Center
Children's Hospital Center
Cincinnati, Ohio

Eleanor G. Goines
Project Manager
DePaul Hospital Sickle Cell Clinic
St. Louis, Missouri

Donald R. Harkness, M.D.
Director, Miami Comprehensive Sickle
Cell Center
Miami, Florida

A. J. Henley
Director, Yeatman Neighborhood Health Center
Sickle Cell Screening and Education Clinic
St. Louis, Missouri

Thomasina Holmes
Program Coordinator
Education, Screening, and Counseling
King Drew Sickle Cell Center
Los Angeles, California

Claire Hurst
Educational Consultant
Rochester, New York

Cynthia Kaufman, M.A.
Instructor in Genetics
University of Bridgeport
Bridgeport, Connecticut

Sylvia L. Lee, P.H.N.
Comprehensive Sickle Cell Center
University of Southern California
Los Angeles, California

Robert I. Levy, M.D.
Director, National Heart, Lung, and Blood
Institute
National Institutes of Health
Bethesda, Maryland

Bertram Lubin, M.D.
Chief, Hematology-Oncology
Children's Hospital Medical Center
Oakland, California

Philip Majerus, M.D.
Hematology Division
Washington University School of Medicine
St. Louis, Missouri

Robert F. Murray, M.D.
Professor of Pediatrics and Medicine
Chief, Medical Genetics Unit
Howard University School of Medicine
Washington, D.C.

Ronald Nagel, M.D.
Associate Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York

Howard Pearson, M.D.
Professor of Pediatrics
Yale University School of Medicine
New Haven, Connecticut

Robert Penny, M.D.
Associate Professor of Pediatrics
University of Southern California
Medical Center
Los Angeles, California

Darleen Powars, M.D.
Associate Professor of Pediatrics
University of Southern California
Medical Center
Los Angeles, California

Maurice F. Rabb, M.D.
Director, Comprehensive Sickle Cell Center
University of Illinois
Chicago, Illinois

Helen Ranney, M.D.
Professor of Medicine
University Hospital
San Diego, California

Clarice D. Reid, M.D.
Coordinator, National Sickle Cell Disease
Program
National Institutes of Health
Bethesda, Maryland

Robert S. Rhodes, M.D.
Associate Professor of Medicine
Meharry Medical College
Nashville, Tennessee

Carl D. Robinson, M.D.
Director, Sickle Cell Screening and
Education Clinic
Flint-Goodridge Hospital
New Orleans, Louisiana

David Satcher, M.D.
Director, Comprehensive Sickle Cell Center
Martin Luther King, Jr., Hospital
Los Angeles, California

Graham Serjeant, M.D.
Director, Epidemiological Research Unit
University of the West Indies
Jamaica, West Indies

Jeanne Smith, M.D.
Director, Comprehensive Sickle Cell Center
Harlem Hospital Center
New York, New York

Louis Sullivan, M.D.
Dean, Medical Education Program
Morehouse College
Atlanta, Georgia

Charles Whitten, M.D.
Director, Comprehensive Sickle Cell Center
Children's Hospital of Michigan
Detroit, Michigan

Sylvia Wooten, M.D.
Medical Officer
Department of Human Resources
Washington, D.C.

*U.S. GOVERNMENT PRINTING OFFICE : 1978 O-722-019/836